Utah Medicaid Pharmacy and Therapeutics Committee

Drug Class Review

Newer Platelet-Aggregation Inhibitors

20:12.18 Platelet-Aggregation Inhibitors

Cangrelor (*Kengreal*)
Clopidogrel (*Plavix, generic*)
Prasugrel (*Effient, generic*)
Ticagrelor (*Brilinta*)
Ticlopidine (*Generic*)
Vorapaxar (*Zontivity*)

28:08.04.24 Salicylates and 24:12.92 Vasodilating Agents, Miscellaneous

Aspirin/extended-release dipyridamole *(Aggrenox, generic)*

Final Report

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Executive Summary

Introduction: Antiplatelet agents inhibit platelet aggregation and prevent coronary artery thrombus formation. This report reviews the comparative efficacy and safety of seven newer antiplatelet products available in the United States: cangrelor, clopidogrel, prasugrel, ticagrelor, ticlopidine, vorapaxar, and a fixed-dose combination containing aspirin plus extended-release dipyridamole (aspirin/XR dipyridamole). These antiplatelet products are indicated for the short- and long-term management after acute coronary syndromes (ACS), for the secondary prevention of thrombotic cardiovascular events in patients with a history of ischemic stroke or transient ischemic attack (TIA), and for the management of symptomatic peripheral arterial disease (PAD).

Cangrelor, clopidogrel, prasugrel, ticagrelor, and ticlopidine are $P2Y_{12}$ receptor inhibitors indicated for patients undergoing percutaneous coronary intervention (PCI) following an ACS event. Clopidogrel and ticagrelor are also indicated in patients with ACS managed medically without undergoing PCI. Clopidogrel has been demonstrated to be effective in the management of ACS and is the most commonly used oral $P2Y_{12}$ receptor inhibitor. However, compared to the newer oral $P2Y_{12}$ receptor inhibitors (ticagrelor and prasugrel), clopidogrel has a delayed onset of action, lower platelet inhibition potency, and insufficient antiplatelet response for some patients with genetic polymorphisms of CYP2C19 and drug interactions.

Dual antiplatelet therapy (DAPT) combining an oral $P2Y_{12}$ receptor inhibitor with aspirin, remains the gold standard drug strategy to reduce the risk of cardiovascular death, myocardial infarction (MI), stroke, and stent thrombosis in patients with ACS. The 2016 American College of Cardiology/American Heart Association (ACC/AHA) guideline strongly recommends maintenance therapy with clopidogrel, prasugrel, or ticagrelor (as DAPT) for at least 12 months following ACS. Based solely on evidence from a single randomized controlled trial (RCT), the guidelines give a moderate level of preference for the use of ticagrelor over clopidogrel (both with aspirin) in ACS patients after coronary stenting implantation, and in non-ST elevation acute coronary syndrome (NSTE-ACS) patients managed medically only. With evidence from a single RCT, a moderate level of preference for the use of prasugrel over clopidogrel (both with aspirin) is specified for ACS patients undergoing PCI who do not present with bleeding risk complications or history of stroke. Guidelines recommend starting DATP as soon as possible after diagnosis and up to 12 months.

For the secondary prevention of stroke, the 2014 American Heart Association/American Stroke Association (AHA/ASA) guideline recommends aspirin, clopidogrel or aspirin/XR dipyridamole, without giving any preference of one product over another.

For the management of PAD, the 2011 American College of Cardiology Foundation/ American Heart Association (ACCF/AHA) guideline recommends aspirin or clopidogrel monotherapy as treatment options for symptomatic PAD. Aspirin plus clopidogrel may be considered in specific situations. Vorapaxar is not yet incorporated in clinical guidelines.

Efficacy: Following a systematic literature search for head-to-head comparisons among newer antiplatelet products, 21 efficacy/safety publications (17 systematic reviews/meta-analyses

[SR/MA] and 4 publications of 3 RCTs) were identified. The majority evaluated the incidence of major adverse cardiac events (MACE), all-cause mortality, MI, or stroke as efficacy endpoints, and the bleeding rates as safety endpoint, except 3 MAs that only evaluated safety outcomes. Efficacy and safety findings included the following:

Acute Coronary Syndromes:

- *Clopidogrel versus ticagrelor or prasugrel*

The efficacy and safety of prasugrel versus clopidogrel and ticagrelor compared to clopidogrel is based on limited evidence, with only one phase III RCT for each comparison (TRITON-TIMI 38 study and PLATO study, respectively). These trials demonstrated superior efficacy outcomes but higher incidence of bleeding adverse events with prasugrel or ticagrelor compared to clopidogrel.

In the TRITON-TIMI 38 trial, prasugrel showed a 19% relative reduction in the risk of cardiovascular death, nonfatal MI, or nonfatal stroke (primary composite endpoint) compared to clopidogrel in patients undergoing PCI following an ACS event (ST-elevation myocardial infarction [STEMI] or NSTE-ACS) at 15 months. For the secondary outcomes; lower rates of MI, stent thrombosis and urgent target-vessel revascularization were also reported with prasugrel compared to clopidogrel; however, no differences between the treatment groups were found in overall reduction of all-cause mortality, cardiovascular mortality, or stroke at 15 months. An increased incidence of overall bleeding and non-coronary artery bypass grafting (CABG) related bleeding was reported in the prasugrel group compared to clopidogrel group. Bleeding events included life-threatening bleeding. Two meta-analyses evaluating the overall ACS population (STEMI and NSTE-ACS) undergoing PCI showed results consistent with those already reported in the pivotal RCT.

In the PLATO study, ticagrelor was more efficacious than clopidogrel for the prevention of cardiovascular-related death, MI, or stroke (primary efficacy outcome) in patients with ACS (STEMI or NSTE-ACS) managed medically or with coronary revascularization at 12 months. Ticagrelor showed a 16% relative reduction in the rate of the primary efficacy outcome, without increasing the incidence of overall major bleeding, but increasing the rates of non-CABG related bleeding. Lower rates of cardiovascular mortality, all-cause mortality, and stent thrombosis were also reported with ticagrelor compared to clopidogrel. As demonstrated with the PLATO study, comparable results were reported in several meta-analyses assessing the overall population with ACS (STEMI and NSTE-ACS).

- *Prasugrel versus ticagrelor*

One RCT conducted in patients with ACS undergoing PCI reported no differences between prasugrel and ticagrelor in the incidence of all-cause death, MI, stroke, serious bleeding, or revascularization at day 7 and month 12. Study limitations raised concerns about the robustness of the results. Two meta-analyses including this weak RCT reported similar efficacy and safety results to those reported in the RCT.

Ticlopidine, alone or combined with aspirin, is rarely used due to its hematologic toxicity. Ticlopidine should only be used when other antiplatelet agents are not tolerated.

Secondary prevention of stroke**:**

For the secondary prevention of stroke, evidence from 3 RCTs in patients with a history of stroke or TIA showed similar efficacy for reducing vascular events or recurrent strokes with clopidogrel compared to ticlopidine, aspirin/XR dipyridamole, or clopidogrel plus aspirin. In each trial clopidogrel showed a better safety profile versus the comparators. Higher rates of major bleeding events were reported with aspirin/XR dipyridamole or clopidogrel plus aspirin compared to clopidogrel monotherapy.

Vorapaxar is a PAR-1 inhibitor currently approved in combination with aspirin and/or clopidogrel for the prevention of ischemic events in stable patients with a history of MI or symptomatic PAD. It should not be used in patients within 2 weeks of the ACS event. Vorapaxar has only been evaluated in placebo-controlled trials. Data providing head-to-head comparisons of vorapaxar with other antiplatelet agents are lacking. Vorapaxar may be considered for selected patients in combination with aspirin and/or clopidogrel.

Adverse Drug Reactions: Newer antiplatelet drugs are associated with high risk of bleeding, including life-threatening bleeding events. Prasugrel, ticagrelor, and vorapaxar include a black box warning concerning the risk of bleeding, and are contraindicated in patients with active pathological bleeding (e.g. intracranial hemorrhage). Prasugrel and vorapaxar are contraindicated in patients with history of TIA or stroke due to risk of major bleeding events. Use of ticagrelor and vorapaxar should be avoided with strong CYP3A inhibitors or inducers. Clopidogrel has a black box warning regarding the potential for reduced efficacy in patients with reduced-function genotype variants (CYP2C19 poor metabolizers). Ticlopidine has a black box warning stating the agent may cause life-threatening hematologic reactions.

Summary: Direct head-to-head evidence in patients with ACS indicates ticagrelor and prasugrel are more effective in reducing cardiovascular ischemic events compared to clopidogrel; however, they are associated with higher rates of bleeding adverse events. Evidence for prasugrel versus ticagrelor suggests similar efficacy and safety results between groups; however limitations of the evidence require further studies.

Aspirin/XR dipyridamole, clopidogrel, clopidogrel plus aspirin and ticlopidine are similarly efficacious in the secondary prevention of stroke, but clopidogrel monotherapy shows a more favorable safety profile. Ticlopidine, alone or combined with aspirin, is rarely used due to its hematologic toxicity. Data providing head-to-head comparisons of vorapaxar compared to other antiplatelet agents are lacking.

Overall, limited direct evidence is available comparing the newer antiplatelet agents. The optimal choice of an antiplatelet agent should be based on careful evaluation of the benefit-risk ratio, individual patient characteristics, medical history, patient´s bleeding risk, and patient preferences. Treatment duration should also be tailored considering ischemic and bleeding risks.

Introduction

Antiplatelet agents inhibit platelet aggregation and prevent coronary artery thrombus formation. Patients diagnosed with ischemic heart disease, stroke or symptomatic peripheral arterial disease (PAD) may require antiplatelet drugs to reduce the risk of thrombotic cardiovascular events (cardiovascular death, myocardial infarction, or stroke). Historically, aspirin has been the gold standard antiplatelet agent based on a large body of evidence demonstrating its efficacy in reducing the frequency of major cardiovascular events.[1-3] More recently, new antiplatelet agents used as adjuncts or substitutes for aspirin have been developed.[1-3] This report reviews the comparative efficacy and safety of seven newer antiplatelet products for the management of acute coronary syndromes (ACS), symptomatic peripheral arterial disease (PAD), and in the secondary prevention of stroke or transient ischemic attack (TIA): cangrelor, clopidogrel, prasugrel, ticagrelor, ticlopidine, vorapaxar, and a fixed-dose combination of aspirin plus extended-release (XR) dipyridamole.

Cangrelor, clopidogrel, prasugrel, ticagrelor, and ticlopidine are $P2Y_{12}$ receptor inhibitors labeled for use in patients undergoing percutaneous coronary intervention (PCI) following an ACS event (myocardial infarction or unstable angina). Clopidogrel and ticagrelor are also indicated in patients with ACS managed medically without undergoing PCI. Most $P2Y_{12}$ receptor inhibitors are recommended as dual antiplatelet therapies (DAPT) in conjunction with aspirin after an ACS event. Clopidogrel, ticlopidine, and aspirin/extended-release (XR) dipyridamole are approved for the secondary prevention of stroke. Clopidogrel and vorapaxar (protease-activated receptor-1 inhibitor agent) are approved for the management of symptomatic PAD. Vorapaxar is also labeled to prevent thrombotic events in patients with a history of MI.

Each of the antiplatelet products is an oral formulation administered once or twice daily, except cangrelor, which is an intravenous injection. Cangrelor is not prescribed in the primary care setting, so it is outside the scope of this report. However, some specific data from systematic reviews were included in this report for informational purposes.

Appendix A provides a summary of the available antiplatelet drug classes. **Table 1** provides specific information concerning labeled indications and dosing recommendation for the platelet-aggregation inhibitor products included in this report. **Table 2** includes product comparisons according to the labeled indications.

Table 1. Platelet-Aggregation Inhibitor Products[4-10]

Generic Name & Approval Date	Brand Name (availability of generic) & Preparations	Indication & Dosage**
$PY2Y_{12}$ Inhibitor Products		
Cangrelor* 2015	Kengreal Single-use 50 mg/vial as a lyophilized powder for reconstitution (IV use)	**Labeled Indication**: - As an adjunct to PCI to reduce the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor **Unlabeled Indications**: - Bridging therapy prior to cardiac surgery **Adult Dose**: - 30 mcg/kg IV bolus prior to PCI followed immediately by a 4 mcg/kg/min IV infusion for at least 2 hours or duration of procedure, whichever is longer - To maintain platelet inhibition after discontinuation of cangrelor infusion, an oral $P2Y_{12}$ platelet inhibitor should be administered (e.g. ticagrelor 180 mg at any time during cangrelor infusion, prasugrel 60 mg after discontinuation of cangrelor, clopidogrel 600 mg after discontinuation of cangrelor)

Clopidogrel
 	
1997
	Plavix (*generic available*)
	
	Oral tablets:
	• 75 mg
	• 300 mg
		Labeled Indication:
		- ACS: To reduce the rate of MI and stroke in patients with:
		  ○ UA/NSTEMI, including patients who are to be managed medically or with coronary revascularization
		  ○ STEMI, including patients who are to be managed medically
		- History of recent MI, recent stroke, or established PAD
		Unlabeled Indications:
		- Adjunctive therapy to support reperfusion with primary PCI
		- Atrial fibrillation (primary prevention of thromboembolism)
		- CABG surgery (secondary prevention)
		- Non-ST-elevation ACS in patients with allergy or major gastrointestinal intolerance to aspirin
		- PCI, non-acute coronary syndrome (i.e. stable ischemic heart disease)
		- Peripheral artery percutaneous transluminal angioplasty
		- Secondary prevention of CVD (patients with diabetes and an aspirin allergy)
		- Symptomatic carotid artery stenosis (including recent carotid endarterectomy)
		Adult Dose:
		- ACS: single 300-mg oral loading dose; then continue at 75 mg QD. Patients should also take *aspirin*
		- Recent MI, or stroke, or established PAD: 75 mg QD orally without a loading dose

Prasugrel
 	
2009
	Effient (*generic available*)
	
	Oral tablets:
	• 5 mg
	• 10 mg
		Labeled Indication:
		- To reduce thrombotic cardiovascular events (including stent thrombosis) in patients with ACS who are to be managed with PCI as follows:
		  ○ Patients with UA/NSTEMI
		  ○ Patients with STEMI when managed with either primary or delayed PCI
		Adult Dose:
		- Single 60-mg oral loading dose; then continue at 10-mg QD. Consider 5-mg QD for patients <60 kg
		- Patients should also take *aspirin* (75-mg to 325-mg) daily

Table 1. Platelet-Aggregation Inhibitor Products[4-10]

Generic Name & Approval Date	Brand Name (availability of generic) & Preparations	Indication & Dosage**
Ticagrelor 2011	Brilinta Oral tablets: • 60 mg • 90 mg	**Labeled Indication**: - To reduce the rate of cardiovascular death, MI, and stroke in patients with: o ACS or a history of MI**.** For at least the first 12 months following ACS, it is superior to clopidogrel. - Ticagrelor also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS **Unlabeled Indications**: - Non-ST-elevation ACS, aspirin intolerant patient **Adult Dose:** - Initial dose: 180 mg oral loading dose following ACS event; then 90 mg BID during the first year after an ACS; after 1 year administer 60mg BID - Use ticagrelor with a daily maintenance dose of *aspirin* of 75-100 mg
Ticlopidine 1991	*Only generic available* Oral tablets: • 250 mg	**Labeled Indication**: - Stroke: To reduce the risk of thrombotic stroke (fatal or nonfatal) in patients who have experienced stroke precursors, and in patients who have had a completed thrombotic stroke. Because ticlopidine is associated with a risk of life-threatening blood dyscrasias including TTP, neutropenia/agranulocytosis and aplastic anemia, ticlopidine should be reserved for patients who are intolerant or allergic to aspirin therapy or who have failed aspirin therapy - Coronary artery stenting: As adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation **Adult Dose:** - Stroke: 250 mg BID - Coronary artery stenting: 250 mg BID with antiplatelet doses of *aspirin* up to 30 days of therapy following successful stent implantation
PAR-1 Inhibitor Products		
Vorapaxar 2014	Zontivity Oral tablets: • 2.08 mg	**Labeled Indication** - History of MI or PAD: To reduce thrombotic cardiovascular events in patients with a history of MI or with PAD **Adult Dose**: - One tablet orally QD - Use with *aspirin* and/or *clopidogrel* according to their indications or standard of care
Antiplatelet Combinations		
Aspirin/ XR-dipyridamole 1999	Aggrenox (*generic available*) Oral capsules: • 25 mg aspirin and 200mg XR-dipyridamole	**Labeled Indication** - To reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis **Adult Dose**: - One capsule BID

*Data included for informational purposes to provide a more comprehensive overview of antiplatelet drugs
** Refer to additional dosing guidance for renal and hepatic impairment in Table 5
Abbreviations: ACS, Acute coronary syndrome; BID, twice daily; CABG, Coronary artery bypass graft (CABG); CVD, cardiovascular disease; IV, intravenous; MI, myocardial infarction; NSTEMI, non–ST-elevation myocardial infarction; PAD, peripheral arterial disease; PAR, protease-activated receptor-1; PCI, percutaneous coronary intervention; QD, once daily; TTP, thrombotic thrombocytopenic purpura; UA, unstable angina, XR-extended-release

Table 2. Product Comparisons Regarding FDA-Approved Indications[4-10]

Platelet-Aggregation Inhibitor Products	FDA Approved Indications						
	ACS				Secondary prevention after MI, stroke, or established PAD		
	PCI		No PCI		Stroke	MI	PAD
	STEMI	NSTEMI/UA	STEMI	NSTEMI/UA			
$P2Y_{12}$ Inhibitor Products							
Clopidogrel		X	X	X	X	X	X
Prasugrel	X	X			CI		
Ticagrelor	X	X	X	X			
Ticlopidine	X	X			X		
Cangrelor*	X	X					
PAR-1 inhibitor Products							
Vorapaxar					CI	X	X
Antiplatelet Combinations							
Aspirin/XR-dipyridamole					X		

* Data included for informational purposes to provide a more comprehensive overview of antiplatelet drugs

Abbreviations: ACS, Acute Coronary Syndrome; CI, contraindication; MI, Myocardial infarction; NSTEMI: Non-ST segment elevation myocardial infarction; PAD, peripheral arterial disease; PAR, protease-activated receptor-1; PCI, Percutaneous Coronary intervention; STEMI: ST segment elevation myocardial infarction; UA: Unstable angina; XR, extended-release

Disease Overview

Cardiovascular disease is the most common cause of death in the United States and is among the rapidly growing health problems throughout the world.[11,12 13-20] Included diseases are (1) coronary artery disease (stable and unstable angina, nonfatal MI, and coronary death),[11] also known as coronary heart disease or ischemic heart disease, (2) ischemic stroke, (3) transient ischemic attack,[11] and (4) peripheral arterial disease (PAD). Some risk factors include a sedentary lifestyle, unhealthy diet, tobacco use, obesity, hypertension, high cholesterol and glucose levels.[12,21] According to the "*Heart Disease and Stroke Statistics-2017 Update*" report from the American Heart Association (AHA), in 2013 coronary heart disease was the first leading cause of mortality worldwide (31.5% of all global deaths), followed by stroke.[12] In the U.S, from 2014 to present, heart disease ranks number 1 and stroke number 5.[12,22,23] Similarly, heart disease and stroke were the number 1 and 4 leading causes of mortality, respectively, in Utah in 2013.[24] Each day in the United States, over 2,200 Americans (219.9 per 100,000 each year) die of a cardiovascular disease (averaging one death every 40 seconds), although cardiovascular mortality has decreased from 1979 to 2014 in the U.S.[12] Data from the Utah Department of Health showed a reduction in the mortality rate of coronary heart disease from 1999 to 2015, in both the U.S. and Utah.[25] With regard to the main indications concerning the antiplatelet products included in this report, the following U.S. epidemiological data is relevant:

- ACS (MI and unstable angina): each year approximately 790,00 Americans experience a MI (one person with a heart attack every 40 seconds), with 580,000 cases being a first MI and 210,000 cases being second MI.[26]
- Stroke: each year 795,000 Americans experience a stroke (averaging one person with a stroke event every 40 seconds), with 610,000 being first or new stroke events and 185,000 recurrent strokes.[12] One person dies of a stroke every 4 minutes.[12] Stroke is the fifth leading cause of death in the United States, killing one person every four minutes.[22,23] Women and African-Americans have a higher incidence of stroke
- PAD: Around 8.5 million Americans are diagnosed with PAD in the U.S.[27] Data from 2003 to 2011 document a substantial increase in the prevalence of peripheral artery disease.[12]

Acute Coronary Syndromes

Acute Coronary Syndrome (ACS) is a group of ischemic coronary heart diseases mainly caused by atherosclerotic plaque rupture, platelet aggregation and thrombus formation.[20,28] ACS signs and symptoms include, acute chest pain, chest tightness, pain radiation to the left arm and/or jaw, abnormalities on the electrocardiogram, and elevated cardiac markers.[20] ACS comprises three disorders: unstable angina (UA), ST-segment elevation myocardial infarction (STEMI), and non-ST elevation myocardial infarction (NSTEMI). Due to the similar pathophysiology and management approach for UA and NSTEMI disorders, both conditions are commonly encompassed into one disorder (i.e. NSTE-ACS, formerly known as UA/NSTEMI).[29] STEMI is characterized per electrocardiogram by an ST-segment elevation, while NSTE-ACS may present with T-wave inversions or ST-segment depressions.[20,28,29] UA and NSTEMI differ in the presentation of cardiac biomarkers of necrosis; NSTEMI presentations include increased

cardiac biomarkers.[29] ACS is an urgent condition that should be rapidly diagnosed, with rapid intervention and treatment. Depending on the ACS subtype diagnosed, the management of ACS may involve medical therapy alone (without coronary intervention) or a reperfusion strategy (e.g. percutaneous coronary intervention [PCI] or fibrinolytic therapy) plus adjunctive treatment with antiplatelet agents.[20,28] PCI is the most common strategy for revascularization in patients with coronary artery disease (CAD), and may be accompanied by the implantation of stents (e.g. bare-metal stents [BMS] or drug-eluting stents [DES].[20]

Stable ischemic heart disease (e.g. stable angina) is a condition with different symptoms, prognosis, and management than acute coronary syndromes.

Stroke

A stroke or cerebrovascular events occurs from insufficient blood circulation to the brain due to a clot or blood vessel rupture.[22] It is a life-threating disease and a leading cause of long-term disability in the United States.[22] The main signs and symptoms of a stroke include paralysis on one side of the body, vision impairment, behavioral changes, and memory loss.[22] There are three different types of stroke: ischemic stroke caused by a blood vessel occlusion (clots); hemorrhagic stroke produced by blood vessel rupture; and transient ischemic attach (TIA) or "mini-stroke" caused by a temporary clot.[22] The most commonly reported stroke type is ischemic stroke (87% of all stroke cases), which includes cerebral thrombosis and cerebral embolism.[22] Stroke can be classified according to the origin of disease, as non-cardioembolic stroke (brain origin) or cardioembolic stroke (thrombus formation in the heart).

Peripheral Arterial Disease

PAD involves the blockage of blood circulation to the extremities, especially to the legs. Atherosclerosis is the main cause of PAD.[27]

Guidelines Recommendations and Treatment Strategies

Therapeutic approaches to prevent cardiovascular disease include lifestyle modification (weight reduction, physical activity, smoking cessation), blood pressure control, lipid-lowering treatment, and use of antiplatelet agents.[13-19]

Acute Coronary Syndromes (STEMI, NSTE-ACS)

Guidelines developed by the American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology (ESC) strongly recommend short- and long-term (up to 12 months) **dual antiplatelet therapy** (DAPT) after an ACS event (with or without PCI). DAPT refers to combinations of two complimentary agents: aspirin and a $P2Y_{12}$ receptor inhibitor agent (e.g. ticagrelor, clopidogrel, or prasugrel). The most commonly $P2Y_{12}$ inhibitor agent used after an ACS has been clopidogrel (oral formulation; approved in 1997); however, it has several limitations (delayed onset of action and platelet response variability).[30-32] Thus, newer $P2Y_{12}$ inhibitor agents were developed: prasugrel (oral formulation; approved in 2009), ticagrelor (oral formulation; approved in 2011), and cangrelor (intravenous injection;

approved in 2015).[30,33] Among the oral formulations, prasugrel and ticagrelor are characterized by higher potency of platelet inhibition and a quicker onset of action than clopidogrel.[33,34]

The *2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease*[35] strongly recommends clopidogrel, prasugrel, or ticagrelor (as DAPT) in patients with ACS after coronary stent implantation and clopidogrel or ticagrelor (as DAPT) in patients with ACS medically treated for at least 12 months (strong recommendation). The guideline gives preference to ticagrelor plus aspirin over clopidogrel plus aspirin in patients with an ACS event (STEMI or NSTE-ACS) undergoing coronary stent implantation and in patients with a NSTE-ACS event who are managed with medical therapy alone (moderate recommendation). Prasugrel is preferred over clopidogrel, both combined with aspirin, in patients undergoing PCI who do not have bleeding risk or history of TIA or stroke (moderate recommendation).[35]

The short-term treatment goals for patients with ACS includes (a) prompt restoration of normal blood flow in the infarcted area, (b) elimination of ischemic signs and symptoms, and (c) mortality reduction, and (d) prevention of recurrent ischemia or MI.[20] Long-term treatment goals involve the management of cardiovascular risks, prevention of repeated MI or stroke events, and quality of life improvement.[20]

Guidelines suggest starting DATP as soon as possible after diagnosis regardless of treatment approach (PCI, fibrinolysis, or medical therapy). The optimal duration of DAPT after ACS is being extensively investigated and debated.[36] Each antiplatelet therapy should be individualized based on benefit/risk balance assessment and clinical and procedural risk factors (e.g. elderly patients, diabetes mellitus, increased bleeding risk, stent-related risks, etc).[35] The 2016 ACC/AHA guideline recommends DAPT for at 12 months after ACS (strong recommendation).[35] DAPT treatment beyond 12 months may be considered in patients with high ischemic risk and low bleeding risk (weak recommendation).[35] Shorter-duration DAPT may be appropriate in patients with low risk of ischemic events and high bleeding risk. A DAPT score tool has been developed to help guide decision-making on the duration of use for DAPT.[35]

Specific guideline recommendations together with the strength of evidence supporting treatment recommendations are outlined in **table 3** (section pertaining to "ACS").

Secondary Prevention of Stroke

The American Heart Association/American Stroke Association (AHA/ASA) has developed guidelines for patients with acute ischemic stroke, for the primary prevention of stroke,[37] and for the secondary prevention of stroke and transient ischemic attack.[38] "*Antiplatelet regimens other than aspirin and cilostazol are not recommended for the prevention of a first stroke*".[37] In patients who have experienced a **non-cardioembolic ischemic stroke or transient ischemic stroke**, the AHA/ASA recommends aspirin monotherapy (50-325 mg/day), the combination of aspirin plus XR dipyridamole (200 mg twice daily), or clopidogrel monotherapy (75 mg daily) after the stroke (strong recommendation for aspirin and aspirin/XR dipyridamole, and moderate recommendation for clopidogrel).[38] Selection of oral antiplatelet therapy should be based on tolerance to these agents and comorbidities. Clopidogrel plus aspirin may be considered for

initial therapy within 24 hours after a stroke and up to 21 days (weak recommendation). However, clopidogrel plus aspirin is not recommended for long-term secondary prevention after a stroke due to the higher bleeding risk compared to monotherapy.[38] Ticlopidine is effective for secondary prevention stroke, but it is associated with hematologic toxicity (e.g. neutropenia/ agranulocytosis and thrombotic thrombocytopenic purpura).[33,38] Ticlopidine should only be used when other antiplatelet agents are not tolerated.[33,38]

Specific guideline recommendations together with the strength of evidence supporting the recommendations are outlined in **table 3** (section pertaining to "Secondary Prevention of Stroke").

Peripheral Artery Disease

Clopidogrel and vorapaxar are currently approved for treatment of PAD. Vorapaxar is a PAR-1 inhibitor, is indicated in combination with aspirin and/or clopidogrel for the secondary prevention in stable patients with history of MI or with symptomatic PAD. Vorapaxar is not recommended for ACS due to an unfavorable benefit/risk balance.

The 2011 ACCF/AHA guideline on peripheral artery disease management[39] recommend aspirin or clopidogrel as aspirin alternative. In patients with PAD who are at high risk and do not have a high risk of bleeding, the guideline recommends clopidogrel plus aspirin.[39] Guidelines for PAD do not currently include treatment recommendations for varapaxar.

Specific guideline recommendations together with the strength of evidence supporting the recommendations are outlined in **table 3** (section pertaining to "Peripheral Artery Disease").

Table 3. Guidelines Including Antiplatelet Agents for the FDA-Approved Indications

Guideline	Recommendation	
Acute Coronary Syndromes		
2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease[35]	**Patients with ACS (NSTE-ACS or STEMI) after coronary stent implantation**	SOR/LOE*
	- In patients with ACS (NSTE-ACS or STEMI) treated with DAPT after BMS or DES implantation, $P2Y_{12}$ inhibitor therapy (**clopidogrel, prasugrel, or ticagrelor**) should be given for **at least 12 months**	Class I; LOE B-R
	- It is reasonable to use **ticagrelor in preference to clopidogrel** for maintenance $P2Y_{12}$ inhibitor therapy after coronary stent implantation[40,41]	Class IIa; LOE B-R
	- It is reasonable to choose **prasugrel over clopidogrel** for maintenance P2Y12 inhibitor therapy in patients with ACS (NSTE-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at risk for bleeding complications and who do not have a history of TIA or stroke[42,43]	Class IIa; LOE B-R
	- In patients who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT (clopidogrel, prasugrel, or ticagrelor) for longer than 12 months may be reasonable	Class IIb; LOE A-SR
	- In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial	Class IIb; LOE C-LD

Table 3. Guidelines Including Antiplatelet Agents for the FDA-Approved Indications

Guideline	Recommendation	
	surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 6 months may be reasonable)	
	- **Prasugrel should not be administered to patients with a prior history of stroke or TIA**[42]	Class III; LOE B-R
	Patients with ACS managed with medical therapy alone	
	- In patients with ACS who are managed with **medical therapy alone** (without revascularization or fibrinolytic therapy) and treated with DATP, P2Y12 inhibitor therapy (clopidogrel or ticagrelor) should be continued for **at least 12 months**	Class I; LOE B-R
	- In patients with **NSTE-ACS** who are managed with **medical therapy alone** (without revascularization or fibrinolytic therapy), it is reasonable to use **ticagrelor in preference to clopidogrel** for maintenance P2Y12 inhibitor therapy[41,44]	Class IIa; LOE B-R
	- In patients who have tolerated DAPT without bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT for longer than 12 months may be reasonable	Class IIb; LOE A-SR
	General recommendations	
	- In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended	Class I; LOE B-NR
	Note: *The Class IIa preferential recommendations for ticagrelor 90 mg twice daily and for prasugrel 10 mg once daily (compared with clopidogrel) in the 2014 Non–ST-Elevation Acute Coronary Syndromes (NSTE-ACS) guideline are continued in this focused update and are now included in relevant PCI and ST-Elevation Myocardial Infarction (STEMI) recommendations, as well*	
2016 European Guidelines on cardiovascular disease prevention in clinical practice[45]		SOR/LOE*
	- In acute coronary syndromes, a $P2Y_{12}$ inhibitor for 12 months is recommended in addition to aspirin, unless there are contra-indications such as excessive risk of bleeding	Class I; LOE A
	- $P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk	Class IIb; LOE A
	- $P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of ischemic and bleeding risks of the patient	Class IIb; LOE A
	- In the chronic phase (>12 months) after MI, aspirin is recommended	Class I; LOE A
	- Prasugrel is not recommended in patients with stable CAD. Ticagrelor is not recommended in patients with stable CAD without a previous ACS	Class III; LOE C
	- Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding.	Class III; LOE B
2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute		SOR/LOE*
	- Clopidogrel loading dose followed by daily maintenance dose in patients unable to take aspirin	Class I, LOE B
	- $P2Y_{12}$ inhibitor, in addition to aspirin, for **up to 12 months** for patients treated initially with either an early invasive or initial ischemia guided strategy. Options include:	Class I, LOE B

Table 3. Guidelines Including Antiplatelet Agents for the FDA-Approved Indications

Guideline	Recommendation	
Coronary Syndromes[29]	○ Clopidogrel: 300-mg or 600-mg loading dose, then 75 mg daily	Class I, LOE B
	○ Ticagrelor: 180-mg loading dose, then 90 mg twice daily	Class I, LOE B
	- $P2Y_{12}$ inhibitor therapy before PCI (loading dose) and continued for at least 12 months (maintenance dose) in patients with NSTE-ACS undergoing PCI with coronary stenting (BMS or DES). Options include:	Class I, LOE B
	○ Clopidogrel: 600-mg loading dose, then 75 mg daily	Class I, LOE B
	○ Prasugrel: 60 mg loading dose, then 10 mg daily	Class I, LOE B
	○ Ticagrelor: 180-mg loading dose, then 90 mg twice daily	Class I, LOE B
	- **Ticagrelor in preference to clopidogrel** for patients with NSTE-ACS treated with an **early invasive or ischemia-guided strategy**[41,44]	Class IIa, LOE B
	- **It is reasonable to choose prasugrel over clopidogrel** for $P2Y_{12}$ treatment in patients with NSTE-ACS who undergo PCI who are not at high risk of bleeding complications[42,46]	Class IIa, LOE B
	- Continuation of DAPT beyond 12 months may be considered in patients undergoing stent implantation	Class IIb, LOE C
	- Prasugrel should not be administered to patients with a prior history of stroke or transient ischemic attack	Class III, LOE B
2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction[47]	**Primary PCI for STEMI patients**	SOR/LOE*
	- $P2Y_{12}$ inhibitor therapy before PCI (loading dose as early as possible or at time of primary PCI) and continued for at least 12 months (maintenance dose) in patients with STEMI undergoing PCI with coronary stenting (BMS or DES). Options include:	Class I, LOE B
	○ Clopidogrel: 600-mg loading dose, then 75 mg daily	Class I, LOE B
	○ Prasugrel: 60 mg loading dose, then 10 mg daily	Class I, LOE B
	○ Ticagrelor: 180-mg loading dose, then 90 mg twice daily	Class I, LOE B
	- Continuation of a P2Y12 inhibitor beyond 1 year may be considered in patients undergoing DES placement.	Class IIb, LOE C
	- Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack	Class III, LOE B
	PCI after fibrinolytic therapy	
	- Clopidogrel should be provided as follows: • A 300-mg loading dose should be given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy (Level of Evidence: C); • A 600-mg loading dose should be given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy • A dose of 75 mg daily should be given after PCI	Class I, LOE C
	- Prasugrel, in a 60-mg loading dose, is reasonable once the coronary anatomy is known in patients who did not receive a previous loading dose of clopidogrel at the time of administration of a fibrinolytic agent, but prasugrel should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non–fibrin-specific agent	Class IIa, LOE B

Table 3. Guidelines Including Antiplatelet Agents for the FDA-Approved Indications

Guideline	Recommendation	
	- Prasugrel, in a 10-mg daily maintenance dose, is reasonable after PCI	Class IIa, LOE B
	- Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack	Class III, LOE B
Primary and Secondary Prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines[36] (2012)	* *Guideline focuses on long-term administration of antithrombotic drugs designed for primary and secondary prevention of cardiovascular disease* - **Primary prevention** of CV: low-dose aspirin (75-100 mg/d) in patients aged >50 years (without symptomatic cardiovascular disease) is recommended over no aspirin therapy - **Established CAD** (patients 1-year post-acute coronary syndrome, with prior revascularization, coronary stenosis . 50% by coronary angiogram, and/or evidence for cardiac ischemia on diagnostic testing): long-term low-dose aspirin or clopidogrel (75 mg/d) - Patients in the first year after **ACS who have not undergone PCI:** • DATP: ticagrelor 90 mg twice daily plus low-dose aspirin 75-100 mg daily or clopidogrel 75 mg daily plus low-dose aspirin 75-100 mg daily) is preferred over single antiplatelet therapy • **Ticagrelor** 90 mg twice daily plus low-dose aspirin **is preferred over clopidogrel** 75 mg daily plus low-dose aspirin - Patients in the first year after **ACS who undergo PCI** with stent placement: • DATP with low-dose aspirin in combination with ticagrelor 90 mg BID, clopidogrel 75 mg/d, or prasugrel 10 mg/d is suggested over single antiplatelet therapy • **Ticagrelor** 90 mg twice daily plus low-dose aspirin **is preferred over clopidogrel** 75 mg daily plus low-dose aspirin - Patients undergoing elective **PCI** with stent placement: Duration of treatment: • Aspirin (75-325 mg/d) and clopidogrel for a minimum duration of 1 month (bare-metal stents) or 3 to 6 months (drug-eluting stents) • Continue low-dose aspirin plus clopidogrel for 12 months for all stents. Thereafter, single antiplatelet therapy is recommended over continuation of dual antiplatelet therapy	
2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention[48]	In patients receiving a stent (BMS or DES) during PCI for ACS, P2Y12 inhibitor therapy should be given for at least 12 months. Options include: • clopidogrel 75 mg daily[49]	Class I, LOE B
	• prasugrel 10 mg daily[42]	Class I, LOE B
	• ticagrelor 90 mg twice daily[41]	Class I, LOE B
Other Guidelines	- 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery - 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery - Canadian Cardiovascular Society, "The Use of Antiplatelet Therapy in the Outpatient Setting: Canadian Cardiovascular Society Guidelines," 2011	

Table 3. Guidelines Including Antiplatelet Agents for the FDA-Approved Indications

Guideline	Recommendation	
Secondary Prevention of Ischemic Stroke		
Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack. A Guideline for Healthcare Professionals (AHA/ASA; 2014)[38]		SOR/LOE*
	- For patients with <u>non-cardioembolic ischemic stroke or TIA</u>, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events	Class I; LOE A
	- **Aspirin monotherapy** (50–325 mg/d) or combination of **aspirin/XR-dipyridamole** (25 mg/200 mg BID) are indicated as initial therapy after TIA or ischemic stroke for prevention of future stroke	Class I; LOE A Class I; LOE B
	- **Clopidogrel monotherapy** (75 mg) is a reasonable option for secondary prevention of stroke in place of aspirin or combination aspirin/dipyridamole. This recommendation also applies to patients who are allergic to aspirin	Class IIa; LOE B
	- The selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics	Class I; LOE C
	- The combination of **aspirin and clopidogrel** might be considered for **initiation** within 24 hours of a minor ischemic stroke or TIA and for continuation **for 21 days**	Class IIb; LOE B
	- The combination of **aspirin and clopidogrel**, when initiated days to years after a minor stroke or TIA and continued for 2 to 3 years, increases the risk of hemorrhage relative to either agent alone and **is not recommended for routine long-term secondary prevention after ischemic stroke or TIA**	Class III; LOE A
2016 European Guidelines on cardiovascular disease prevention in clinical practice[45]		SOR/LOE*
	- In patients with non-cardioembolic ischaemic stroke or TIA, prevention with **aspirin only**, or **dipyridamole plus aspirin or clopidogrel alone** is recommended	Class I; level A
	- In patients with non-cardioembolic cerebral ischaemic events, anticoagulation is not recommended.	Class III; level B
Antithrombotic and Thrombolytic Therapy for Ischemic Stroke, 2012	- In patients with a history of noncardioembolic ischemic stroke or TIA, we recommend long-term treatment with aspirin (75-100 mg once daily), **clopidogrel** (75 mg once daily), **aspirin/extended-release dipyridamole** (25 mg/200 mg bid), or **cilostazol** (100 mg bid) over no antiplatelet therapy (Grade 1A), oral anticoagulants (Grade 1B) , the combination of **clopidogrel plus aspirin** (Grade 1B) , or triflusal (Grade 2B) .	
Peripheral Artery Disease		
2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (Updating the 2005 Guideline)[39]		SOR/LOE*
	- **Clopidogrel** (75 mg per day) is recommended as an effective alternative antiplatelet therapy to aspirin to reduce the risk of MI, stroke, or vascular death in individuals with atherosclerotic lower extremity PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia (Level of Evidence: B)	Class I, LOE B
	- The combination of **aspirin and clopidogrel** may be considered to reduce the risk of cardiovascular events in patients with symptomatic atherosclerotic lower extremity PAD, including those with intermittent	Class IIb, LOE B

Table 3. Guidelines Including Antiplatelet Agents for the FDA-Approved Indications

Guideline	Recommendation
	claudication or critical limb ischemia, prior lower extremity revascularization (endovascular or surgical), or prior amputation for lower extremity ischemia and who are not at increased risk of bleeding and who are at high perceived cardiovascular risk. (Level of Evidence: B)
2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases in collaboration with ESVS[50]	- In patients requiring antiplatelet therapy, clopidogrel may be preferred over aspirin - DAPT with aspirin and clopidogrel for at least 1 month should be considered after infra-inguinal stent implantation - DAPT with aspirin and clopidogrel may be considered in below-the-knee bypass with a prosthetic graft - Because of a lack of proven benefit, antiplatelet therapy is not routinely indicated in patients with isolated asymptomatic LEAD
Antithrombotic therapy for peripheral artery occlusive disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition), 2008[51]	*"For secondary prevention in patients with symptomatic PAD, we recommend one of the two following antithrombotic regimens to be continued long term over no antithrombotic treatment:* - *Aspirin 75 to 100 mg daily or **clopidogrel** 75 mg daily (all Grade 1A)* - *We suggest not to use dual antiplatelet therapy with aspirin plus clopidogrel (Grade 2B)"*

Abbreviations: ACC/AHA, American College of Cardiology/American Heart Association; ACS, acute coronary syndrome; AHA/ASA, American Heart Association/American Stroke Association; BID, twice daily; BMS, bare-metal stents; CAD, coronary artery disease; CV, cardiovascular disease; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stents; ESC, European Society of Cardiology; ESVS, European Society for Vascular Surgery; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic stroke; XR, extended-release

*__Strength of recommendations (SOR)__:

Class I: Strong recommendation for therapy as useful, effective, and beneficial (Use is recommended/indicated)

Class IIa: Moderate recommendation for therapy as useful, effective, and beneficial (Treatment use is reasonable)

Class IIb: Weak recommendation for therapy; may be considered but, effectiveness is not well established

Class III (Harm): Strong recommendation against therapy; do not use

Note: Refer to full guideline for further information concerning the levels of evidence and strength of recommendation

*__Levels of Evidence (LOE)__:

Level of Evidence A: Data derived from multiple randomized clinical trials, meta-analyses, or systematic review (SR) from an Evidence Review Committee

Level of Evidence B: Data derived from a single randomized trial (R) or nonrandomized studies (NR)

Level of Evidence C: Limited data (LD), expert opinion (EO), case studies, or standard of care

Pharmacology & Special Populations

Antiplatelet agents can inactivate platelet aggregation by multiple mechanisms, including (1) antagonism of the platelet $P2Y_{12}$ ADP receptor that may be irreversible (e.g. thienopyridines: clopidogrel, prasugrel, ticlopidine) or reversible (e.g. nonthienopyridines: ticagrelor, cangrelor), (2) inhibition of the protease-activated receptor 1 (PAR-1) [e;g. vorapaxar[52]], and (3) combination of additive effects (platelet cyclooxygenase-1 inhibition with aspirin plus adenosine reuptake inhibition into the platelet with dipyridamole).[33]

Differences among antiplatelet agents involve metabolism, receptor binding characteristics, platelet activity recovery, antiplatelet potency, onset of action, drug interactions, and safety profiles. Clopidogrel and prasugrel are prodrugs requiring biotransformation to their active metabolites via cytochrome P450 in order to exert their action on platelets.[33,35,52] Clopidogrel requires a 2-step hepatic activation via CYP2C19, whereas prasugrel requires a single step via several CYP450 enzymes.[32] Ticagrelor and cangrelor are not prodrugs and block the target receptor directly.[22,24] Unlike clopidogrel and prasugrel, which are irreversible $P2Y_{12}$ receptor inhibitors, ticagrelor and cangrelor bind reversibly to the $P2Y_{12}$ receptor, resulting in faster platelet function recovery after drug discontinuation.[33] Clopidogrel has been used for years as part of DAPT in patients with ACS. Nonetheless, several studies have reported non-responsiveness to clopidogrel in up to 40% of patients, putting these patients at a higher risk of recurrent cardiovascular events.[31,32] The mechanisms leading to insufficient antiplatelet response to clopidogrel may include genetic factors (reduced effect in CYP2C19 poor metabolizers), clinical factors (e.g. poor adherence, drug interactions with CYP2C19 inhibitors), and cellular factors.[31,53]

Among the advantages of the newer antiplatelet agents compared to clopidogrel, ticagrelor, prasugrel and cangrelor demonstrate more potent platelet inhibition and a shorter onset of action than clopidogrel.[31,33] However, they exhibit an increased risk of bleeding events compared to clopidogrel.[32]

Table 4 outlines pharmacokinetic information for antiplatelet products. **Table 5** outlines special population considerations for the antiplatelet agents. **Table 6** outlines drug-drug interaction concerns.

Table 4. Pharmacokinetics for Antiplatelet Products[4-10,33]

Antiplatelet Products	Onset of action (IPA)	Peak effect	Metabolism	Excretion	Half-life
P2Y12 Inhibitor Products					
Cangrelor*	2 min	2 min	Rapidly inactivated in the circulation by dephosphorylation (metabolism independent of hepatic function) Metabolite: a nucleoside, which has negligible anti-platelet activity	Urine (58%); feces (35%)	3 to 6 minutes

Table 4. Pharmacokinetics for Antiplatelet Products[4-10,33]

Antiplatelet Products	Onset of action (IPA)	Peak effect	Metabolism	Excretion	Half-life
Clopidogrel	• 300-600 mg loading dose: IPA within 2 hours • 50-100 mg/day: IPA detected by the second day of treatment	• 300-600 mg loading dose: 20-37% IPA at 6 hours • 50-100 mg/day: 50% to 60% IPA at 5-7 days	**Prodrug** Extensively hepatic: • via esterase-mediated hydrolysis to a carboxylic acid derivative (inactive) • via CYP450-mediated (**CYP2C19** primarily) oxidation to a thiol metabolite (active)	Urine (50%) Feces (46%)	Parent drug: 6 h Active metabolite: 30min Inactive metabolite: 8 h
Prasugrel	60 mg loading dose: <30 minutes (median time to reach ≥20% IPA: 30 minutes	60 mg loading dose: 79-84% mean IPA at 4 hours	**Prodrug** Rapid intestinal and serum metabolism: • via esterase-mediated hydrolysis to a thiolactone intermediate (inactive), which is then converted, via CYP450-mediated (primarily **CYP3A4 and CYP2B6**) oxidation, to an active metabolite	Urine (~68% inactive metabolites) Feces (27% inactive metabolites)	7 h (range 2-15h)
Ticagrelor	180 mg loading dose: 41% within 30 minutes (similar to clopidogrel 600 mg at 8 hours)	180 mg loading dose: ~80% at 2 hours	Hepatic via **CYP3A4/5** to active metabolite	Feces (58%) Urine (26%) - amount of parent drug and active metabolite excreted in urine <1%	7 h
Ticlopidine	6 hours	3-5 days	Extensively hepatic At least 1 active metabolite	Urine (60%) Feces (23%)	13 h
PAR-1 Inhibitor Products					
Vorapaxar	1 week (≥80% IPA)	1-2 hours	Hepatic via CYP3A4 and CYP2J2. Major active metabolite: M20	Feces (58%) Urine (25%) Primarily in the form of metabolites	3 -4 days
Antiplatelet Combinations					
Aspirin/ dipyridamole	ASA: N/A Dipy: N/A	ASA: 1 h (0.5 to 2 h) Dipy: 2 h (1 to 6h)	ASA: hepatic; hydrolysis Dipy: Hepatic; metabolite: glucuronic acid conjugate	ASA: Renal Dipy: Biliary	ASA: 20-60 min Dipy: 10 h

*Data included for informational purposes to provide a more comprehensive overview of antiplatelet drugs
Abbreviations: ASA, aspirin; dipy, dipyridamole; h, hour; IPA, inhibition of platelet aggregation; N/A, not available

Table 5. Special Population Considerations for Antiplatelet Products[4-10,33]

Antiplatelet Products	Age	Adjustment for Kidney Disease	Adjustment for Hepatic Disease	Pregnancy/Lactation
$P2Y_{12}$ Inhibitor Products				
Cangrelor*	No pediatric indication No dose adjustments based on age (≥65 years) are necessary	No dosage adjustment is necessary	No dosage adjustment is necessary	Pregnancy: Adverse events were observed in some animal reproduction studies Lactation: It is not known if cangrelor is excreted in breast milk
Clopidogrel	No pediatric indication No dose adjustments based on age (≥65 years) are necessary	No dosage adjustment is necessary Experience is limited in patients with severe and moderate renal impairment	No dosage adjustment is necessary in patients with hepatic impairment	Pregnancy: Reproduction studies performed in rats and rabbits revealed no evidence of impaired fertility or fetotoxicity Clopidogrel should be used during pregnancy only if clearly needed Lactation: a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother
Prasugrel	No pediatric indication ≥75 years: Risk of bleeding, and effectiveness is uncertain in patients ≥75 years of age. Use of prasugrel is generally not recommended in these patients, except in high-risk situations (diabetes and past history of myocardial infarction)	No dosage adjustment is necessary Experience is limited in patients with end-stage renal impairment (patients at higher risk of bleeding)	No dosage adjustment is necessary in patients with mild to moderate hepatic impairment No studies are conducted in patients with severe hepatic impairment (patients at higher risk of bleeding)	Pregnancy: No structural malformations were observed in animal reproductive and developmental toxicology studies Due to the mechanism of action of prasugrel, and the associated identified risk of bleeding, consider the benefits and risks of prasugrel and possible risks to the fetus Lactation: the decision to continue or discontinue breast-feeding during therapy should take into account the risk of infant exposure, the benefits of breast-feeding to the infant, and benefits of treatment to the mothe
Ticagrelor	No pediatric indication No dose adjustments based on age (≥65 years) are necessary	No dosage adjustment is necessary	Mild impairment: No dosage adjustment is necessary Moderate impairment: not studied. Use with caution (ticagrelor is metabolized by the liver) Severe impairment: Avoid use	Pregnancy: Adverse events have been observed in animal reproduction studies. Ticagrelor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Lactation: Due to the potential for serious adverse reactions in the nursing infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother.

Table 5. Special Population Considerations for Antiplatelet Products[4-10,33]

Antiplatelet Products	Age	Adjustment for Kidney Disease	Adjustment for Hepatic Disease	Pregnancy/Lactation
Ticlopidine	No pediatric indication Elderly: A dosage decrease may be necessary if bleeding develops	No dosage adjustment is reported Bleeding time may be prolonged in patients with moderate renal impairment	Mild to moderate hepatic impairment: No dosage adjustment is reported. Use with caution Severe hepatic impairment: Avoid use	Pregnancy: Teratogenic effects have not been observed in animal reproduction studies Lactation: Due to the potential for serious adverse reactions in the nursing infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of treatment to the mother
PAR-1 Inhibitor Agents				
Vorapaxar	No pediatric indication Elderly: Because older patients are generally at a higher risk of bleeding, consider patient age before initiating vorapaxar	No dosage adjustment is necessary	Mild to moderate hepatic impairment: No dosage adjustment is necessary Severe hepatic impairment: Avoid use	Pregnancy: Adverse events have not been observed in animal reproduction studies. Vorapaxar should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus Lactation: Due to the potential for serious adverse reactions in the nursing infant, discontinue nursing or discontinue vorapaxar
Antiplatelet Combinations				
Aspirin/ dipyridamole	No pediatric indication Elderly: Use caution or avoid use as potentially inappropriate in older adults	GFR ≥10 mL/min: no dosage adjustment GFR <10 mL/min: Avoid use	Mild to moderate hepatic impairment: no dosage adjustments Severe hepatic impairment: Avoid use	Pregnancy: Avoid aspirin/dipyridamole during the third trimester of pregnancy Lactation: Caution should be exercised when administering aspirin/dipyridamole to nursing women.

*Data included for informational purposes to provide a more comprehensive overview of antiplatelet drugs
Abbreviations: PAR, protease-activated receptor-1

Table 6. Labeled Drug Interactions for Antiplatelet Products[4-10,33]

Antiplatelet Products	Drug Interactions
$P2Y_{12}$ Inhibitor Products	
Cangrelor	• **Thienopyridines:** Do not administer clopidogrel or prasugrel during cangrelor infusion. If clopidogrel or prasugrel are administered during cangrelor infusion, they will have no antiplatelet effect until the next dose is administered. Clopidogrel and prasugrel, therefore, should not be administered until cangrelor infusion is discontinued
Clopidogrel	• **CYP2C19 Inhibitors**: avoid concomitant use of clopidogrel with CYP2C19 inhibitors because it results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition. Avoid concomitant use of clopidogrel with **omeprazole or esomeprazole** • **NSAIDs, warfarin, SSRIs, SNRIs**: clopidogrel increases risk of bleeding • **Repaglinide** (CYP2C8 substrates): clopidogrel increases substrate plasma concentrations

Table 6. Labeled Drug Interactions for Antiplatelet Products[4-10,33]

Antiplatelet Products	Drug Interactions
Prasugrel	• **Warfarin and NSAIDs**: prasugrel increases risk of bleeding • Prasugrel can be administered with other drugs: inducers or inhibitors of cytochrome P450 enzymes, aspirin (75-mg to 325-mg per day), heparin, GPIIb/IIIa inhibitors, statins, digoxin, and drugs that elevate gastric pH, including PPI and H blockers
Ticagrelor	• **Strong CYP3A inhibitors:** Avoid use with strong CYP3A inhibitors (ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin) because ticagrelor exposure is increased • **Strong CYP3A inducers**: Avoid use with strong CYP3A inducers (rifampin, phenytoin, carbamazepine and phenobarbital) because ticagrelor exposure is reduced • **Aspirin**: ticagrelor effectiveness is reduced with aspirin maintenance doses above 100 mg • **Simvastatin or lovastatin**: Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse effects • **Digoxin**: Monitor digoxin levels with initiation of or any change in ticagrelor.
Ticlopidine	Substrate of CYP3A4 (major) • **Aspirin and Other NSAIDs**: Ticlopidine potentiates the effect of aspirin or other NSAIDs on platelet aggregation. Long-term concomitant use of aspirin and ticlopidine is not recommended • **Antacids**: Administration of ticlopidine after antacids resulted in an 18% decrease in plasma levels of ticlopidine • **Cimetidine**: Chronic administration of cimetidine reduced the clearance of a single dose of ticlopidine hydrochloride by 50% • **Digoxin**: Coadministration of ticlopidine with digoxin resulted in a slight decrease (approximately 15%) in digoxin plasma levels • **Theophylline**: significant increase in the theophylline elimination half-life from 8.6 to 12.2 hours and a comparable reduction in total plasma clearance of theophylline • **Phenytoin**: Several cases of elevated phenytoin plasma levels with associated somnolence and lethargy have been reported following coadministration with ticlopidine
PAR-1 Inhibitor Agents	
Vorapaxar	• **Strong CYP3A inhibitors:** Avoid concomitant use of vorapaxar with strong CYP3A inhibitors • **Strong CYP3A inducers**: Avoid concomitant use of vorapaxar with strong CYP3A inducers
Antiplatelet Combinations	
Aspirin/ dipyridamol	• Co-administration with **anticoagulants, antiplatelets, or NSAIDs** can increase risk of bleeding • Decreased renal function can occur with co-administration with **NSAIDs**

*Data included for informational purposes to provide a more comprehensive overview of antiplatelet drugs

Abbreviations: NSAID, nonsteroidal anti-inflammatory drugs; PAR, protease-activated receptor-1; PPI, proton pump inhibitors; SSRI, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors

Methods

Literature Search

Search strategies were developed by an Informational Scientist for OVID Medline and EMBASE. Strategies consisted of controlled vocabulary, such as MeSH, and keyword phrases. Two methodological filters were used, one for systematic reviews and another for randomized controlled trials (RCT). Results were limited to English language. Databases were searched from 2010 to present for SR/MAs and from 2015 to present for RCTs. In EMBASE, we excluded conference abstracts. Searches were conducted in October, November, and December 2017. The complete search strategies and terms are available in **Appendix B**.

We also screened the reference lists of related systematic reviews and other relevant websites for further information:

1. For guidelines addressing ACS management, stroke prevention, and PAD management: websites of The American College of Cardiology (ACC)/American Heart Association (AHA), The American Stroke Association, and The European Society of Cardiology.
2. For prescribing information package inserts: The Food and Drug Administration website (Drugs@FDA: FDA Approved Drug Products: https://www.accessdata.fda.gov/scripts/cder/daf/)
3. Evidence-based drug information databases (Micromedex, Lexicomp, and UpToDate)

Screening

At least two review authors screened titles and abstracts. Conflicts were resolved via discussion between reviewers or a third person. The full texts for all citations receiving two inclusion votes were retrieved; screening and inclusion were determined by the lead author. **Figure 1** shows the PRISMA flow chart[54] for the review process.

Inclusion and Exclusion Criteria

Systematic reviews/meta-analyses (SR/MA) of RCTs and RCTs providing direct head-to-head efficacy and/or safety comparisons among the antiplatelet products were included. For product comparisons where a systematic review provided robust data, we examined only those trials or systematic reviews published after the search date of the robust systematic review. For inclusion in the report, studies (SR/MAs or RCTs) had to have as primary efficacy endpoints the incidence of major cardiovascular events (MACE), all-cause mortality, MI, or stroke, and as a primary safety endpoint the bleeding rates. Safety studies showing comparative data among antiplatelet agents were also included.

Excluded references met the following exclusion criteria:

- SR/MAs not reporting separate results for each antiplatelet agent (i.e. results of novel $P2Y_{12}$ including prasugrel and ticagrelor versus clopidogrel) were excluded
- SR/MAs including observational studies, registries, and retrospective studies in the pooled analyses. Only results from MA of RCTs were considered for the report

- Reviews not using systematic review methodology
- Network meta-analyses: according to the hierarchy of evidence, the quality of network meta-analyses is downgraded because they include indirect comparisons
- Studies comparing the antiplatelet agents included in this report (alone or combined with aspirin) versus aspirin alone or placebo
- Single studies such as observational studies, pharmacodynamic studies, studies evaluating non-FDA approved doses, registries, pilot studies, switching studies, or studies evaluating biological outcomes
- RCTs evaluating cangrelor. Only SR/MAs including cangrelor were considered for this review

A list containing the excluded references is provided in **Appendix G**.

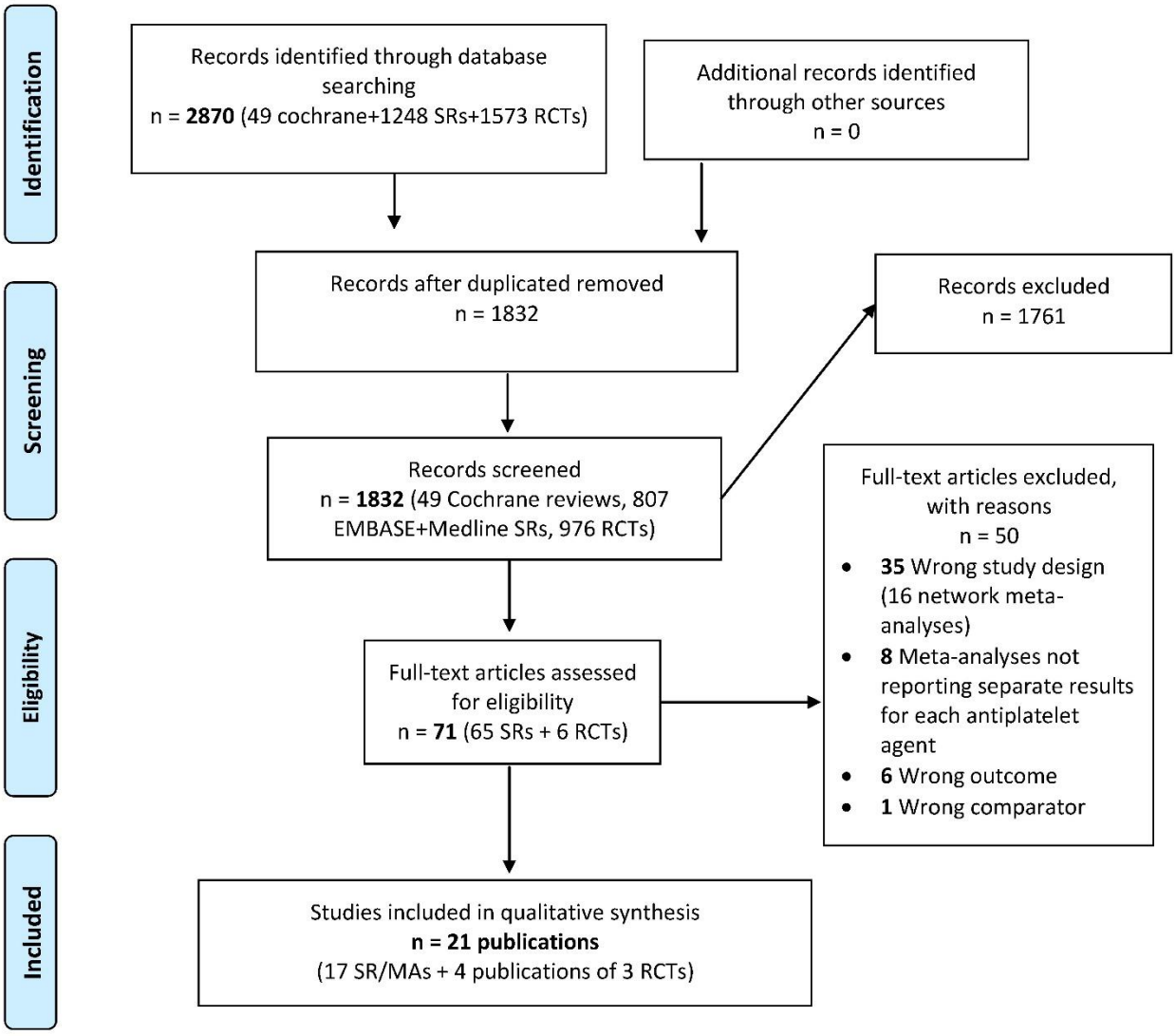

Figure 1. PRISMA Flow Diagram of the selection process

Clinical Efficacy and Safety

After applying inclusion and exclusion criteria, 21 publications (17 SR/MAs, 3 RCTs) evaluating the comparative efficacy and safety of the antiplatelet agents listed in **Table 1** were included in the qualitative synthesis. Results from one of the RCTs identified were reported in 2 publications. Several MAs evaluated more than one head-to head antiplatelet drug comparison within the study. All studies evaluated the incidence of MACE, all-cause mortality, MI, or stroke as efficacy endpoints, and bleeding rates as safety endpoint, with the exception of 3 MAs that only evaluated safety outcomes. Most identified MAs included RCTs. Some MAs also included pharmacodynamics studies reporting the outcomes of interest as secondary endpoints.

For the **management of acute coronary syndromes**, the following publications were identified:

- 4 publications[30,55-57] (4 SR/MAs) comparing clopidogrel versus prasugrel.
- 5 publications[30,55,56,58,59] (5 SR/MAs) comparing clopidogrel versus ticagrelor
- 2 publications[60,61] (2 SR/MAs) comparing prasugrel versus ticagrelor
- 6 publications[30,55,62-65] (6 SR/MAs) comparing clopidogrel versus cangrelor. These MAs were included for informational purposes. We did not performed a systematic literature search for RCTs including cangrelor
- 3 publications[66-68] (3 SR/MAs) evaluating safety outcomes
- 1 additional head-to-head RCT (clopidogrel versus ticagrelor) not included in previous MAs was identified.[69] Furthermore, three publications[70-72] of 2 RCTs were identified in the RCT search. However, these RCTs were already included in some MAs. Key RCTs were identified from the references listed in the SR/MAs selected

For the **secondary prevention of stroke**, the following publications were identified:

- 1 publication[73] (1 SR/MA including 3 single studies for 3 different antiplatelet drug comparisons: 1 RCT comparing clopidogrel versus ticlopidine, 1 RCT comparing clopidogrel versus aspirin/XR dipyridamole, 1 RCT comparing clopidogrel plus aspirin versus clopidogrel). Results from each single study were extracted
- 1 publication[74] (1 SR/MA) evaluating ticagrelor and prasugrel in patients with history of stroke (non FDA approved indication)
- No new head-to-head RCTs within the last two years were identified. Key RCTs were identified from the references listed in the SR/MAs identified

For the **management of peripheral artery disease**, SR/MAs comparing available therapies (i.e. clopidogrel and vorapaxar) for PAD are lacking and no head-to-head RCTs within the last two years were identified. With regard to vorapaxar, only placebo-controlled trials were identified. The majority of trials with clopidogrel included aspirin or placebo as main comparators.

Appendixes C, D, E, and F include evidence tables outlining characteristics of included SR/MA (**Appendix C**), efficacy and safety results for the MAs identified (**Appendix D**),

efficacy and safety results for the key RCTs included in previous MAs (**Appendix E**), and efficacy and safety results for one RCT not included in previous MA (**Appendix F**).

1. Acute Coronary Syndromes (STEMI and NSTE-ACS)

DAPT containing aspirin and a $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel or ticagrelor) was the standard treatment tested in patients with ACS.

- **Clopidogrel versus prasugrel**

Meta-Analyses

The clinical efficacy and safety of clopidogrel versus prasugrel were compared in **4 systematic reviews/meta-analyses (SR/MA)**. Different outcomes were evaluated in each SR/MA. Only results from SR/MAs of RCTs were extracted.

Bae et al[55] **(**2016) reported a significant reduction in the incidence of the primary composite endpoint (all-cause mortality, MI or stroke) with prasugrel compared to clopidogrel in patients with CAD undergoing PCI. The separate endpoint of all-cause mortality was similar between treatment groups. A significant increased risk of non-CABG related major bleeding was noted in the prasugrel group compared to clopidogrel group. The composite endpoint of the net rate of adverse clinical events (primary efficacy and safety endpoints) significantly decreased with prasugrel compared to clopidogrel.

Briasoulis el al[30] (2016) stated a significantly lower risk of MI and stent thrombosis with prasugrel compared to clopidogrel in patients with ACS and/or undergoing PCI. Information regarding other endpoints (i.e. MACEs, all-cause mortality, stroke, and bleeding) was not extracted because the pooled analysis included a study without random assignation to antiplatelet agents.

Bavishi et al[56] (2015) reported no differences in the rates for all the efficacy outcomes (i.e. MACE, MI, cardiovascular death, all-cause mortality, and stroke) between treatment groups in the subgroup of patients with NSTE-ACS. A trend to reduce the incidence of MACE, MI, cardiovascular death, and all-cause mortality was observed with prasugrel compared to clopidogrel (but was not significant). The safety profile in terms of TIMI major bleeding and TIMI minor/major bleeding was significantly more favorable for clopidogrel compared to prasugrel. One of the limitations for the prasugrel versus clopidogrel comparison involves the inclusion of a non-prespecified post-hoc analysis of the TRITON-TIMI 38 (NSTE-ACS subgroup analysis) in the meta-analysis, which increases the risk of bias.

Chen et al[57] (2015) suggested that the risk of MACE outweighed the risk of minor and major bleeding in patients with CAD treated with prasugrel compared with clopidogrel. The meta-analysis pertaining to prasugrel versus standard-dose clopidogrel included 4 RCTs, from which one RCT was performed in Japan and included a lower prasugrel dosage (i.e. 20 mg loading dose and 3.25 mg maintenance dose) than that approved in the U.S.

Table 7. RCTs Included in SR/MAs for Acute Coronary Syndromes: Clopidogrel versus Prasugrel

	RCTs Comparing Clopidogrel vs. Prasugrel					
META-ANALYSES	Wiviott 2007[42], **TRITON-TIMI 38** (STEMI+NSTE-ACS)	Montalescot 2009[43], **TRITON-TIMI 38 subgroup analysis** (STEMI with PCI)	De Servi 2014[75], **TRITON-TIMI 38 subgroup analysis** (NSTE-ACS)	Roe 2012[46], **TRILOGY ACS** (NSTEMI/ UA)	Wiviott 2005[76], **JUMBO–TIMI 26** (NSTE-ACS + SCAD - Phase 2 study)	Saito 2014[77] **PRASFIT ACS** (Japanese study)
Bae 2016[55]	√			√	√	
Briasoulis 2016[30]	√			√	√	
Bavishi 2015[56]			√	√		
Chen 2015[57]	√			√	√	√

Abbreviations: NSTE-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SCAD, stable coronary artery disease; STEMI, ST-elevation myocardial infarction

Randomized Controlled Trials

No additional head-to-head RCTs within the last three years (from 2015 to December 2017) were identified. Results from 2 pivotal RCTs (TRITON TIMI 38 trial and TRILOGY ACS) included in all the relevant MAs will be discussed for a more detailed review of key findings supporting treatment guidelines.

Wiviott et al[42] (2007) conducted a multicenter, international, randomized, double-blind, parallel-group study (**TRITON TIMI 38 trial**) to compare clopidogrel (300 mg loading dose/75 mg maintenance dose once daily) versus prasugrel (60 mg loading dose/10 mg maintenance dose once daily) in 13,608 patients undergoing PCI following an ACS event (STEMI, NSTE-ACS). All patients also received aspirin and follow-up duration was 6 to 15 months. A statistically significant reduction in the primary efficacy endpoint (composite of the rate of cardiovascular death, nonfatal MI, or nonfatal stroke at 15 months) was reported with prasugrel compared to clopidogrel (12.1% with for clopidogrel vs. 9.9% with prasugrel; hazard ratio **(HR) 0.81; 95% CI, 0.73 to 0.90**; ***p*<0.001**). The rates of other endpoints such as MI, urgent target-vessel revascularization, and stent thrombosis were significantly reduced with prasugrel versus clopidogrel at 15 months. No differences were reported between groups regarding overall all-cause mortality, cardiovascular mortality, and stroke at 15 months. Regarding selected subgroups, no net benefit from prasugrel was reported in patients ≥75 years old and patients <60 kg. In the subgroup of patients with a history of stroke or TIA, results for the composite endpoint combining primary efficacy and safety endpoints were worse with prasugrel versus clopidogrel (HR, 1.54; 95% CI, 1.02 to 2.32; *p*= 0.04). The incidence of thrombolysis in myocardial infarction (TIMI) major bleeding not related to CABG, including fatal bleeding, was significantly higher in the prasugrel group compared to clopidogrel group at 15 months (HR 1.32; 95% CI, 1.03 to 1.68; *p*=0.03). Major or minor TIMI bleeding and other types of bleeding were also significantly higher in the prasugrel group compared with clopidogrel group.

Two subgroup analyses of the TRITON TIMI 38 trial were performed in different subgroup populations (STEMI with PCI [**Montalescot 2009**][43] and NSTE-ACS with PCI [**De Servi 2014**][75]). In the subgroup of patients with STEMI undergoing PCI (pre-specified analysis of TRITON TIMI 38 trial) and the subgroup of patients with NSTE-ACS (NSTEMI and UA) undergoing PCI (non-prespecified analysis of TRITON TIMI 38 trial), prasugrel was better than clopidogrel for the primary endpoint (composite of the rate of cardiovascular death, nonfatal MI, or nonfatal stroke at 15 months). In the STEMI subgroup, no differences were reported for non-CABG related TIMI bleeding, whereas in the NSTE-ACS subgroup a significantly higher incidence of non-CABG related TIMI bleeding was noted in the prasugrel group. TIMI bleeding after CABG was significantly increased in the STEMI subgroup.

Overall, the full analysis showed showed a 19% relative reduction in the risk of cardiovascular death, nonfatal MI, or nonfatal stroke (primary efficacy endpoint) with prasugrel compared to clopidogrel. An increased incidence of major bleeding not related to CABG was reported in the prasugrel group compared to clopidogrel group.

Roe et al[46] (2012) performed an RCT (TRILOGY ACS) to compare prasugrel (30 mg loading dose/10 mg daily as maintenance dose) versus clopidogrel (300 mg loading dose/75 mg daily as maintenance dose) in patients with UA/NSTEMI without revascularization. All patients received aspirin. The duration of treatment was 30 months. No between-group difference for the primary endpoint (a composite of cardiovascular death, non-fatal MI, or non-fatal stroke) and the risk of bleeding were reported. A pre-specified subgroup analysis in UA/NSTEMI patients with or without angiography was conducted by **Wiviott et al**[78] (2013). In the prasugrel group, patients who had angiography showed a reduction in the primary endpoint compared to clopidogrel group. It should be noted that this trial evaluated prasugrel for a different indication than that approved by the FDA (i.e. ACS patients undergoing PCI).

- **Clopidogrel versus ticagrelor**

Meta-Analyses

The clinical efficacy and safety of clopidogrel versus ticagrelor were compared in **5 SR/MAs**. Different outcomes were evaluated in each SR/MA. Only results from SR/MAs of RCTs were extracted.

Tan et al[58] (2017) reported no differences between ticagrelor and clopidogrel regarding the incidence of cardiovascular death and stroke in patients with ACS. Information regarding the primary composite endpoint (cardiovascular death, MI, or stroke) was not extracted because the pooled analysis included an observational study.

Yang et al[59] (2017) suggested a significantly lower incidence in all-cause mortality and MI in the ticagrelor group compared with clopidogrel group in patients undergoing PCI. No between-group differences in terms of stroke, total bleeding, and minor/major bleeding were reported.

Bae et al[55] (2016) reported a statistically significant reduction in the incidence of the primary composite endpoint (all-cause mortality, MI or stroke) with ticagrelor compared to clopidogrel in patients with CAD undergoing PCI. The separate endpoint of incidence of all-cause mortality

was similar between treatment groups. Study drug discontinuations due to adverse events were more frequent in the ticagrelor group compared to clopidogrel group. A significant increased risk of non-CABG related major bleeding was noted in the ticagrelor group compared to clopidogrel group. The composite endpoint of the net rate of adverse clinical events (primary efficacy and safety endpoints) significantly decreased with ticagrelor compared to clopidogrel.

Briasoulis el al[30] (2016) stated a significantly lower risk of MACE, all-cause mortality, MI, and stent thrombosis with ticagrelor compared to clopidogrel in patients with ACS and/or undergoing PCI. No differences with respect to the incidence of stroke and major bleeding were reported between treatment groups.

Bavishi et al[56] (2015) reported a statistically significant reduction in the incidence of MACE and MI with ticagrelor compared to clopidogrel in patients with NSTE-ACS. No differences with respect to the incidence of cardiovascular death, all-cause mortality, stroke, TIMI major bleeding, and TIMI major/minor bleeding were reported between treatment groups. One of the limitations for the ticagrelor versus clopidogrel comparison involves the inclusion of a non-prespecified post-hoc analysis of the PLATO study (NSTE-ACS subgroup analysis) in the meta-analysis, which increases the risk of bias.

Table 8. RCTs Included in SR/MA for Acute Coronary Syndromes: Clopidogrel versus Ticagrelor

	RCTs Comparing Clopidogrel vs. Ticagrelor					
META-ANALYSES	Wallentin 2009[41] (**PLATO trial)**	Cannon 2010[79]; **PLATO subgroup analysis** (planned invasive strategy)	Steg 2010[80]; **PLATO subgroup analysis** (STEMI with PCI)	Lindholm 2014[81]; **PLATO subgroup analysis** (NSTE-ACS)	Cannon 2007[82]; **DISPERSE-2** (phase 2 study)	Goto 2015[70]; **PHILO** (Asiatic patients)
Tan 2017[58]	√	√			√	
Yang 2017[59]		√	√			
Bae 2016[55]	√				√	
Briasoulis 2016[30]	√				√	√
Bavishi 2015[56]				√	√	

Abbreviations: NSTE-ACS, non-ST-elevation acute coronary syndrome; RCT, randomized controlled trial; STEMI, ST-elevation myocardial infarction

Randomized Controlled Trials

One additional head-to-head RCTs within the last three years (from 2015 to December 2017) was identified (Tang 2016[69]). In addition, one publication of a single RCT (Goto 2015[70]) was identified in the RCT search; however, this study was already included in a SR/MA and results were not extracted.

Tang et al[69] evaluated the efficacy and safety of ticagrelor compared to clopidogrel in 400 STEMI patients undergoing PCI in China. Results indicated a significantly lower incidence of MACE and the composite enpoint of cardiovascular death, nonfatal MI, and stroke with ticagrelor compared to clopidogrel. No between-group differences were reported for the

individual components of the composite endpoint, all-cause mortality, stent thrombosis, unplanned revascularization, and bleeding risk. Study limitations include small sample size and short follow-up.

Results from 1 pivotal RCT (PLATO study) included in all the relevant SR/MAs will be discussed for a more detailed review of key findings supporting treatment guidelines.

Wallentin et al[41] (2009) performed a multicenter, double-blind, randomized trial (**PLATO study**) to compare ticagrelor (180 mg loading dose, 90 mg twice daily as maintenance dose) with clopidogrel (300 to 600 mg loading dose, 75 mg daily maintenance dose) in 18,624 patients hospitalized with an ACS event (STEMI or NSTE-ACS, with onset of symptoms in the previous 24 hours) and who were either medically treated or managed with medical therapy plus revascularization. All patients also received aspirin. Follow-up period during the study was 12 months. The primary endpoint at 12 months, defined as a composite of death from vascular causes, MI, or stroke, was statistically significantly reduced with ticagrelor compared to clopidogrel (**HR, 0.84; 95% CI, 0.77 to 0.92; *p*<0.001**). Secondary endpoints such as the rate of MI, all-cause mortality, death from vascular causes, and stent thrombosis were also significantly reduced in the ticagrelor group. No between-group differences in the rate of stroke and the incidence of major bleeding (primary safety endpoint) were observed. Ticagrelor was associated with a significant increase in the rate of non-CABG related bleeding (secondary safety endpoint) and dyspnea.

Three pre-specified subgroup analyses of the PLATO study differentiated: 1) patients with ACS and planned invasive strategy (Cannon 2010),[79] 2) patients with STEMI and planned PCI (Steg 2010),[80] and 3) patient with ACS managed without invasive strategy (James 2011).[44]

The first subgroup analysis[79] (**Cannon 2010**) evaluated 13,408 patients with ACS (STEMI or NSTEMI) and planned invasive strategy. As demonstrated with the previous full analysis of PLATO trial, this substudy showed significantly lower rates of cardiovascular death, myocardial infarction, or stroke (primary composite endpoint) in the ticagrelor group compared to the clopidogrel group (HR 0.84, 95% CI 0.75-0.94; p=0.0025). No differences in bleeding adverse events were reported between the treatment groups.

The second subgroup analysis[80] (**Steg 2010**) evaluated 7,544 patients with STEMI and planned PCI. Rates of cardiovascular death, myocardial infarction, or stroke (primary composite endpoint) were lower in the ticagrelor group compared to the clopidogrel group; however, results were not statistically significant (HR, 0.87; 95% CI, 0.75 to 1.01; p=0.07). Secondary outcomes were comparable to the overall PLATO results, with the exception of stroke events that were significantly higher with ticagrelor. No differences in bleeding adverse events were reported between the treatment groups.

The third subgroup analysis[44] (**James 2011**) assessed 5,216 patients with ACS and non-invasive treatment strategy. Similar to the original trial, significantly lower rates of cardiovascular death, myocardial infarction, or stroke (primary composite endpoint) were reported in the ticagrelor group compared to the clopidogrel group (HR 0.85, 95% CI 0.73 to 1.00; p=0.045). Although the incidence in major bleeding and non-CABG related major bleeding

rates was higher in the ticagrelor group, no statistically significant differences were reported between the treatment groups.

Overall, clinical evidence evaluating the efficacy and safety of ticagrelor suggests ticagrelor is more efficacious than clopidogrel for the prevention of cardiovascular-related death, MI, or stroke (primary composite outcome) in patients with ACS (STEMI or NSTE-ACS). In the full analysis, ticagrelor showed a 16% relative reduction in the rate of the primary efficacy outcome, without increasing the incidence of overall major bleeding, but increasing the rates of non-CABG related bleeding events.[41]

- **Prasugrel versus ticagrelor**

The clinical efficacy and safety of prasugrel versus ticagrelor were compared in **2 SR/MAs**. Only results from SR/MAs of RCTs were extracted.

Meta-Analyses

Sakurai et al[60] (2017) suggested comparable rates of death, MI, stroke, stent thrombosis, and bleeding (according to the study criteria) between prasugrel and ticagrelor in patients with ACS who were treated with PCI. Bleeding events considering the TIMI criteria were lower with prasugrel compared with ticagrelor. However, the majority of studies did not evaluate clinical endpoints as primary endpoints, few studies and few number of patients were included altering the power of the meta-analysis, the duration of the included studies was short (up to 6 months), and different definitions of endpoints were used (e.g. bleeding criteria). Larger and longer RCTs are needed to confirm these initial comparative findings.

Watti et al[61] (2017) reported no differences between prasugrel and ticagrelor regarding mortality, MI, stroke, and bleeding (according to study critetia) in the subgroup analysis of RCTs including patients with ACS undergoing PCI. A study limitation is the low number of RCTs comparing prasugrel and ticagrelor. Larger RCTs are needed to confirm these initial comparative findings.

Table 9. RCTs Included in SR/MA for Acute Coronary Syndromes: Prasugrel versus Ticagrelor

	RCTs Comparing Ticagrelor vs. Prasugrel											
MA	Alexopoulos 2013[83]	Alexopoulos 2013[84]	Deharo 2013[85]	Laine 2014[86]	Bonello 2015[87]	Sardella 2015[88]	Motovska 2016[72] (**PRAGUE-18**)	Alexopoulos 2012[89]	Alexopoulos 2012[90]	Parodi 2013[91]	Parodi 2014[92]	Hochholzer 2017[93]
Sakurai 2017[60]	√	√	√	√	√	√	√	√	√	√	√	√
Watti 2017[61]					√		√	√		√		

Abbreviations: MA, meta-analysis; RCT, randomized controlled trial

Randomized Controlled Trials

No additional head-to-head RCTs within the last three years (from 2015 to December 2017) were identified. Two publications of a single RCT (Motovska 2016 and 2017[71,72]) were found in the RCT search; however, this study was already included in the 2 SR/MAs identified. Results from this pivotal RCT (**PRAGUE-18**) will be reviewed to highlight details of the key findings.

Motovska et al[72] (2016) conducted a 12-month randomized controlled trial (PRAGUE-18) to compare prasugrel (60 mg loading dose/10 mg once daily as maintenance dose) versus ticagrelor (180 mg loading dose/90 mg twice daily as maintenance dose) in 1,230 patients with acute myocardial infarction undergoing PCI. No differences were reported between prasugrel and ticagrelor with respect to the primary efficacy endpoint (a composite of all-cause death, reinfarction, stroke, serious bleeding, or urgent target vessel revascularization within 7 days of randomization), key secondary endpoint (composite of cardiovascular death, nonfatal myocardial infarction, or stroke) within 30 days, and bleeding events. However, several limitations are noted. The study was not double-blind, did not describe attrition rate, was underpowered to detect differences between treatment groups, include very wide confidence intervals for the main outcomes, and was early finished due to futility. Larger well-conducted clinical trials comparing prasugrel versus ticagrelor are required. One-year outcomes of the PRAGUE-18 study were published by **Motovska et al**[71] (2017). Consistent results with those reported in the preliminary study were observed. However, patients could switch to clopidogrel due to economic reasons (34% switched from the prasugrel group and 44% from the ticagrelor group).

Ongoing Studies

The ongoing multicenter, randomized, open-label trial (ISAR-REACT 5 - Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment trial)[94] will compare ticagrelor versus prasugrel in patients with ACS and planned invasive strategy.

- **Clopidogrel versus cangrelor**

Meta-Analyses

The clinical efficacy and safety of cangrelor versus clopidogrel were compared in **6 SR/MAs**. Only results from SR/MAs of RCTs were extracted.

Bae et al[55] **(**2016) reported no differences between cangrelor and clopidogrel for the primary composite endpoint (all-cause mortality, MI or stroke) and the risk of non-CABG related major bleeding events in patients with CAD undergoing PCI.

Briasoulis el al[30] (2016) stated a significantly lower risk of major cardiovascular events (MACE) and stroke with cangrelor compared to clopidogrel in patients with ACS undergoing PCI. No differences with respect to the incidence of all-cause mortality, MI, stent thrombosis, and major bleeding were reported between treatment groups.

Tang et al[62] (2015) showed a statistically significant decrease regarding MACE (primary endpoint) and stent thrombosis with cangrelor compared to clopidogrel in patients with CAD undergoing PCI. However, an increase in TIMI minor bleeding and GUSTO (Global utilization

of streptokinase and tissue plasminogen activator for occluded coronary arteries criteria) moderate bleeding were reported in the cangrelor group.

Pandit et al[63] (2014) stated no significant differences between cangrelor and clopidogrel in decreasing the rate of the primary composite endpoint (death, ischemia-driven revascularization, and MI at 48 hours), all-cause mortality, and MI. No differences were found for severe or fatal bleeding. A significant reduction in ischemia-driven revascularization, stent thrombosis, and Qwave MI was seen in the cangrelor group compared to clopidogrel group.

Sardar et al[64] (2014) reported a statistically significant decrease in ischemia-driven revascularization, stent thrombosis, and Qwave MI in the cangrelor group compared to clopidogrel group, without increasing major bleeding. No differences in MI and all-cause mortality were observed between groups. All patients underwent PCI.

Verdoia et al[65] (2014) reported statistically significant reduction in recurrent ischemia symptoms or ischemia-driven revascularization and stent thrombosis with cangrelor compared to clopidogrel in patients with ACS or stable angina undergoing PCI. No statistically significant differences in the endpoints of mortality, nonfatal MI, and TIMI major bleedings were reported between cangrelor and clopidogrel.

Table 10. RCTs Included in SR/MA for Acute Coronary Syndromes: Clopidogrel versus Cangrelor

	RCTs Comparing Clopidogrel vs. Cangrelor			
META-ANALYSES	Bhatt 2009[95]; **CHAMPION PLATFORM 2009**	Bhatt 2013[96]; **CHAMPION PHOENIX, 2013**	Harrington 2009[97]; **CHAMPION PCI, 2009**	Leonardi 2012
Bae 2016[55]	√	√	√	
Briasoulis 2016[30]	√	√	√	
Tang 2015[62]	√	√	√	√
Pandit 2014[63]	√	√	√	
Sardar 2014[64]	√	√	√	
Verdoia 2014[65]	√	√	√	

Abbreviations: RCT, randomized controlled trial

Randomized Controlled Trials

Results from three pivotal RCTs comparing cangrelor versus clopidogrel (CHAMPION PCI,[97] CHAMPION PLATFORM,[95] and CHAMPION PHOENIX[96]) in patients undergoing PCI were combined in the aforementioned meta-analyses.

- **Vorapaxar**

Vorapaxar is a PAR-1 inhibitor currently approved in combination with aspirin and/or clopidogrel for the prevention of ischemic events in stable patients with a history of MI or symptomatic PAD. It should not be used in patients within 2 weeks of an ACS event. Vorapaxar has been only evaluated in placebo-controlled trials. Data providing head-to-head comparisons of vorapaxar compared to other antiplatelet agents are lacking.

2. Secondary Prevention of Stroke

Meta-Analyses

One SR/MA including 3 single studies for 3 different antiplatelet drug comparisons was identified. Results from each single study were extracted.

Kwok et al[73] (2015) evaluated the efficacy of antiplatelet agents for the secondary prevention of stroke after a lacunar stroke. No significant differences were reported between (1) aspirin/XR dipyridamole and clopidogrel (based on PROFESS study[98]), (2) clopidogrel plus aspirin and clopidogrel (based on MATCH study[99]), and (3) ticlopidine and clopidogrel (based on Uchiyama 2009[100]), with respect to stroke, ischemic stroke, or a composite of stroke, MI, and death, respectively.

Table 11. RCTs Included in SR/MA for Secondary Prevention of Stroke

META-ANALYSES	RCTs			
	ASA/dipy vs. ASA+dipy	**Clo vs. ticlo**	**ASA+clo vs. clo**	**ASA+Dipy vs. clo**
	ESPS-2 1992 (Ariesen 2006)	Uchiyama 2009	MATCH (Diener 2004)	PRoFESS 2005 (Sacco 2008)
Kwok 2015[73]	√	√	√	√

Abbreviations: ASA, aspirin; clo, clopidogrel; dipy, dipyridamole; ticlo, ticlopidine

Randomized Controlled Trials

No new head-to-head RCTs within the last three years (from 2015 to December 2017) were identified. Results from the 3 single studies included in the aforementioned MA will be reviewed.

- **Clopidogrel versus ticlopidine**

Uchiyama et al[100] (2009) conducted a double blind, multicenter RCT in Japan to compare ticlopidine versus clopidogrel in patients with a history of stroke (last stroke event within more than 8 days). Clopidogrel showed better safety profile and similar efficacy in terms of vascular events (cerebral infarction, MI, and vascular death) compared to ticlopidine. A significantly lower incidence of hepatic dysfunction was reported with clopidogrel compared to ticlopidine (HR 0.610; 95% CI 0.529, 0.703; p<0.001).

- **Clopidogrel versus aspirin/XR dipyridamole**

Sacco et al[98] (2008) conducted a double-blind factorial trial (PRoFESS study) to compare aspirin/dipyridamole versus clopidogrel in patients with a history of stroke. This study showed similar incidences of recurrent strokes (primary endpoint) between groups (HR 1.01; 95% CI, 0.92 to 1.11). Similar results were also found for the secondary outcome of a composite of stroke, myocardial infarction, or death from vascular causes. A higher rate of major bleeding, especially intracranial hemorrhage was reported with aspirin/dipyridamole compared to clopidogrel.

- **Clopidogrel monotherapy versus clopidogrel plus aspirin**

Diener et al[99] (2004) performed an 18-month RCT (MATCH study) to compare clopidogrel plus aspirin versus clopidogrel in 7,599 patients with prior stroke or TIA. Results for the primary endpoint (a composite of ischemic stroke, MI, vascular death, or prehospitalization for acute ischemia) were similar between treatment groups. Risk of fatal or major bleeding increased with aspirin plus clopidogrel versus clopidogrel alone.

Information for non-FDA indications

Gouya et al[74] (2014) performed a meta-analysis and suggested no differences in the incidence of total stroke, ischemic stroke or TIA, and intracranial hemorrhage between prasugrel and clopidogrel in the overall population with high risk of stroke. In the group of patients who had a history of stroke or TIA (secondary prevention of stroke subgroup), patients treated with prasugrel showed a significantly higher risk of overall stroke (ischemic stroke, TIA, intracranial hemorrhage) compared to those treated with clopidogrel. Currently, prasugrel´s labeling contains a contraindication for use in patients with history of TIA or stroke. **Gouya et al**[74] also conducted a meta-analysis to compare ticagrelor versus clopidogrel. Results suggested no between-group differences in the incidence of total stroke, ischemic stroke or TIA, and intracranial hemorrhage in the overall population with high risk of stroke and in the subgroup of patients who had a history of stroke or TIA (secondary prevention of stroke subgroup). Currently, ticagrelor is not labeled for the prevention of stroke in patients with a history of stroke.

3. Peripheral Arterial Disease

Clopidogrel and vorapaxar are labeled for the treatment of symptomatic PAD. No head-to-head comparisons were identified.

Safety

Overall, contraindications, black box warnings, and drug-drug-interactions are crucial to take into account during the treatment decision-making process. The main safety concern related to antiplatelet drugs is the risk of bleeding.[4-10] This adverse event is the most commonly reported safety endpoint in all studies evaluated. Prasugrel was associated with an increased risk of major bleeding, including life-threatening bleeding events, compared to clopidogrel.[5,42] Ticagrelor and prasugrel increased the incidence of non-CABG related bleeding compared to clopidogrel in 2 large RCTs.[41,42] Prasugrel, ticagrelor, and vorapaxar include bleeding risk in a Black Box Warning.[5,8,10] Before treatment initiation, patient's risk of bleeding should be considered.

Other black box warnings and contraindications are also relevant. Prasugrel and vorapaxar are contraindicated in patients with history of TIA or stroke due to risk of intracranial hemorrhage and stroke. Prasugrel should be used cautiously in patients ≥75 years.[5] Ticagrelor should be combined with aspirin doses lower than 100 mg daily to avoid reduced effect of ticagrelor. Prasugrel and ticagrelor should not be used in patients with active pathological bleeding and in patients planning to undergo an urgent CABG surgery due to the increased risk of bleeding.[5] A lower effect of clopidogrel is expected in CYP2C19 poor metabolizers.[4] Cangrelor infusion should not be used in conjunction with $P2Y_{12}$ inhibitors during the PCI, especially with prasugrel and clopidogrel because their effects are significantly reduced. Cangrelor should be discontinued before starting oral antiplatelet therapy with $P2Y_{12}$ inhibitors.[7]

Ticlopidine has a black box warning stating the agent may cause life-threatening hematologic reactions, including neutropenia, agranulocytosis, thrombotic thrombocytopenia purpura (TTP), and aplastic anemia.[9]

Evidence suggests higher rates of major bleeding events and withdrawal rates with aspirin/XR dipyridamole or clopidogrel plus aspirin compared to clopidogrel monotherapy.[98,99]

Safety comparative evidence from 3 meta-analyses reported (1) no association between thienopyridines and cancer events,[66] (2) a higher risk of dyspnea with reversible $P2Y_{12}$ inhibitors (ticagrelor and cangrelor) compared to irreversible $P2Y_{12}$ inhibitors (prasugrel and clopidogrel),[67] and (3) lower bleeding rates with ticlopidine plus aspirin compared to clopidogrel plus aspirin.[68]

Table 12. Adverse Events and Black Box Warnings for Antiplatelet Products[4-10]

Generic Name & Approval Date	Black Box Warnings/Other Warnings	Adverse Events
$PY2Y_{12}$ Inhibitor Products		
Cangrelor*	*Other warnings:* • Bleeding • Hypersensitivity • Concurrent use with thienopyridines: do not administer clopidogrel or prasugrel until the cangrelor infusion is discontinued	**Hema&onco** Hemorrhage (GUSTO: 16%; TIMI: <1%) **Renal**: Renal insufficiency (3%; severe; creatinine clearance <30 mL/minute) **Respiratory**: Dyspnea (1%)

Table 12. Adverse Events and Black Box Warnings for Antiplatelet Products[4-10]

Generic Name & Approval Date	Black Box Warnings/Other Warnings	Adverse Events
Clopidogrel	*Black box warning:* • **CYP2C19 poor metabolizers**: clopidogrel has a reduced effect on platelet activity in patients with two loss-of-function alleles of the CYP2C19 gene. Tests are available to identify patients who are CYP2C19 poor metabolizers *Other warnings:* • Bleeding • Thienopyridine hypersensitivity • TTP • Lacunar stroke: the use of clopidogrel plus aspirin increase the risk of major hemorrhage and the rate of all-cause mortality • Renal impairment • Lower GI bleed patients • Surgical patients	*1% to 10%:* **GI**: Gastrointestinal hemorrhage (2%) **Hema&onco**: Minor hemorrhage (4% to 5%), major hemorrhage (1% to 4%) *Frequency not defined:* **Hema&onco**: Hematoma **Respiratory**: Epistaxis
Prasugrel	*Black box warning:* • **Bleeding Risk**: • May cause significant, sometimes fatal, bleeding. **Do not use** prasugrel in **patients with active pathological bleeding or a history of TIA or stroke**. • In **patients ≥75 years**, use is generally not recommended due to increased risk of fatal and intracranial bleeding and uncertain benefit, except in high-risk situations (patients with diabetes or a history of MI) in which its effect appears to be greater and its use may be considered. • Surgical patients: Do not initiate therapy in patients likely to undergo **urgent CABG surgery**; when possible, discontinue ≥7 days prior to any surgery; **increased risk of bleeding** *Other warnings:* • Hypersensitivity • TTP • GI disease • Hepatic impairment • Renal impairment • Lower GI bleed patients • Low-weight patients	*1% to 10%:* **CV**: Hypertension (8%), hypotension (4%), atrial fibrillation (3%), bradycardia (3%), peripheral edema (3%) **CNS**: Headache (6%), dizziness (4%), fatigue (4%), noncardiac chest pain (3%) **Derm**: Skin rash (3%) **Endo&meta**: Hypercholesterolemia (≤7%), hyperlipidemia (≤7%) **GI**: Nausea (5%), diarrhea (2%), gastrointestinal hemorrhage (2%) **Hema&onco**: Leukopenia (3%), anemia (2%), major hemorrhage (2%), minor hemorrhage (2%), major hemorrhage (life-threatening: 1%) **NMS**: Back pain (5%), limb pain (3%) **Respiratory**: Epistaxis (6%), dyspnea (5%), cough (4%) **Miscellaneous**: Fever (3%)
Ticagrelor	*Black box warning:* • **Bleeding Risk**: • Ticagrelor increases the **risk of bleeding** including significant and sometimes fatal bleeding. • Use is **contraindicated** in patients with active pathological bleeding (eg, peptic ulcer bleeding, intracranial hemorrhage or history of intracranial hemorrhage). Where possible, manage bleeding without discontinuing ticagrelor as the risk of	*>10%:* **Respiratory**: Dyspnea (14%) *1% to 10%:* **CV**: ECG abnormality (ventricular pause; 2% to 6%), presyncope (≤2%), syncope (≤2%) **CNS**: Dizziness (5%), loss of consciousness (≤2%) **GI**: Nausea (4%)

Table 12. Adverse Events and Black Box Warnings for Antiplatelet Products[4-10]

Generic Name & Approval Date	Black Box Warnings/Other Warnings	Adverse Events
	cardiovascular events is increased upon discontinuation • Surgical patients: Avoid initiation of ticagrelor when **urgent CABG surgery** is planned; when possible, discontinue use at least 5 days before any surgery. • **Aspirin/other NSAIDs**: Maintenance doses of aspirin greater than 100 mg/day reduce the efficacy of ticagrelor and should be avoided *Other warnings:* • Bradyarrhythmias • Hyperuricemia • Respiratory: Dyspnea • Bleeding disorders • Hepatic impairment • Renal impairment • Lower GI bleed patients • Discontinuation of therapy: Premature discontinuation of therapy will increase the risk of MI, stroke, and death	**Hema&onco**: Major hemorrhage (4%), minor hemorrhage (4%) **Renal**: Increased serum creatinine (7%; transient; mechanism undetermined) *Frequency not defined:* **Endo&meta**: Increased uric acid
Ticlopidine	*Black box warning:* • **Life-threatening hematologic toxicity**: neutropenia/agranulocytosis, TTP, aplastic anemia • Monitoring of clinical and hematologic status *Other warnings:* • Thienopyridine hypersensitivity • Bleeding disorders • Hepatic impairment • Renal impairment • Lower GI bleed patients • Coronary artery stents • Elective surgery	*>10%:* **Endo&meta**: Hyperlipidemia (8% to 10%; within 1 month of therapy), increased serum triglycerides **GI**: Diarrhea (13%; may be chronic) *1% to 10%:* **CNS**: Dizziness (1%) **Derma**: Skin rash (5%), pruritus (1%) **GI**: Dyspepsia (7%), nausea (7%), gastrointestinal pain (4%), flatulence (2%), vomiting (2%), anorexia (1%) **Hema&onco**: Neutropenia (2%), purpura (2%) **Hepatic**: Increased serum alkaline phosphatase (>2 x upper limit of normal: 8%), abnormal hepatic function tests (1%)
PAR-1 Inhibitor Products		
Vorapaxar	*Black box warning:* • **Bleeding Risk** (including intracranial hemorrhage and fatal bleeding): Use is **contraindicated** in patients with history of stroke, TIA, or ICH; or active pathological bleeding. *Other warnings:* • Hepatic impairment • Renal impairment	*>10%:* **Hema&onco**: Hemorrhage (any GUSTO bleeding): 25%), major hemorrhage, life-threatening (13%; clinically significant bleeding, including any bleeding requiring medical attention such as intracranial hemorrhage, or clinically significant overt signs of hemorrhage associated with a drop in hemoglobin of ≥3 g/dL [or when hemoglobin is unavailable, an absolute drop in hematocrit of ≥15% or a fall in hematocrit of 9% to <15%]) *1% to 10%:* **CNS**: Depression (2%)

Table 12. Adverse Events and Black Box Warnings for Antiplatelet Products[4-10]

Generic Name & Approval Date	Black Box Warnings/Other Warnings	Adverse Events
		Derma: Skin rash (2%, includes cutaneous eruptions and exanthemas) Endocrine & metabolic: Iron deficiency (<2%) **GI**: Gastrointestinal hemorrhage (4%) **Hema&onco**: Anemia (5%), major hemorrhage (GUSTO bleeding category "moderate or severe": 3%; GUSTO bleeding category "severe": 1%) **Ophthalmic**: Retinopathy (<2%)
Antiplatelet Combinations		
Aspirin/ dipyridamole	*Other warnings:* • Bleeding • GI effects • Hepatic effects • Salicylate sensitivity • Tinnitus • Cardiovascular disease • Ethanol use • Hepatic impairment • Renal impairment • Pediatric: Avoid use in children due to risk of Reye syndrome associated with aspirin • Surgical patients: bleeding risk • Interchangeability: Aspirin/dipyridamole combination product is not interchangeable with the individual components of aspirin and dipyridamole • Lactose/sucrose: Formulation may contain lactose and/or sucrose	*>10%:* **CNS**: Headache (39%; tolerance usually develops) **GI**: Abdominal pain (18%), dyspepsia (18%), nausea (16%), diarrhea (13%) *1% to 10%:* **CV**: Cardiac failure (2%), syncope (1%) Central nervous system: Fatigue (6%), pain (6%), amnesia (2%), malaise (2%), seizure (2%), confusion (1%), drowsiness (1%) **GI**: Vomiting (8%), gastrointestinal hemorrhage (1% to 4%), melena (2%), anorexia (1%), hemorrhoids (1%) **Hema&onco**: Hemorrhage (3%), anemia (2%), rectal hemorrhage (2%), purpura (1%) **NMS**: Arthralgia (6%), back pain (5%), arthritis (2%), weakness (2%), arthropathy (1%), myalgia (1%) **Respiratory**: Cough (2%), epistaxis (2%), upper respiratory tract infection (1%)

*Data included for informational purposes to provide a more comprehensive overview of antiplatelet drugs
Abbreviations: CABG, Coronary artery bypass grafting; CNS, central nervous system; CV, cardiovascular; Derma, dermatologic; endo&meta: endocrine & metabolic; GI, gastrointestinal; GUSTO; Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; hema&Onco; hematologic & oncologic; ICH, intracranial hemorrhage; MI, myocardial infarction; NMS, neuromuscular & skeletal; TIA, transient ischemic attack,TIMI, Thrombolysis in Myocardial Infarction; TTP, Thrombotic thrombocytopenic purpura

Summary

The antiplatelet products are indicated in the management of acute coronary syndrome, revascularization, or symptomatic peripheral arterial disease and in the prevention of ischemic stroke. Following a systematic literature search for head-to-head comparisons among newer antiplatelet products, 21 efficacy/safety publications representing 17 SR/MAs and 3 RCTs were identified. Efficacy and safety findings included the following:

- Prasugrel or ticagrelor showed significantly lower rates of cardiovascular death, nonfatal MI, or nonfatal stroke (primary composite endpoint) compared to clopidogrel in patients with ACS. However, prasugrel and ticagrelor were associated with a higher incidence of bleeding adverse events compared to clopidogrel. Results were based on limited evidence (one single RCT for each comparison and several MAs including the pivotal trials plus additional studies)
- Prasugrel showed no differences in the incidence of all-cause death, MI, stroke, serious bleeding, or revascularization compared to ticagrelor in one single RCT and 2 MAs including ACS patients undergoing PCI. The pivotal trial had several limitations and additional well-conducted studies are required.
- For the secondary prevention of stroke, evidence from 3 RCTs in patients with a history of stroke or TIA showed similar efficacy in reducing vascular events or recurrent strokes with clopidogrel compared to ticlopidine (1 RCT), clopidogrel compared to aspirin/XR dipyridamole (1 RCT), and clopidogrel compared to aspirin plus clopidogrel (1 RCT). In all these trials clopidogrel showed a better safety profile versus the comparators. Higher rates of major bleeding events were reported with aspirin/XR dipyridamole or clopidogrel plus aspirin compared to clopidogrel monotherapy.
- Ticlopidine, alone or combined with aspirin, is rarely used for coronary artery stenting or secondary prevention of stroke due to its hematologic toxicity.
- Vorapaxar is a PAR-1 inhibitor currently approved in combination with aspirin and/or clopidogrel for the prevention of ischemic events in stable patients with a history of MI or symptomatic PAD. Data providing head-to-head comparisons of vorapaxar with other antiplatelet agents are lacking.

Overall, limited direct evidence is available comparing the newer antiplatelet products. The optimal choice of an antiplatelet product should be based on careful evaluation of the benefit-risk ratio, individual patient characteristics, medical history, bleeding risk, and patient preferences. Treatment duration should also be tailored considering ischemic and bleeding risks.

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Appendix A

Table 1. Antiplatelet Agents[28,33]

Oral Administration	Intravenous Administration
○ **COX-inhibitors** *Irreversible*: Aspirin	○ **GP IIb/IIIa receptor antagonists** Abciximab Eptifibatide Tirofiban
○ **$P2Y_{12}$ receptor inhibitors** *Irreversible thienopyridines*: Clopidogrel Prasugrel Ticlopidine *Reversible nonthienopyridines*: Ticagrelor	○ **$P2Y_{12}$ receptor inhibitors** *Reversible nonthienopyridines* Cangrelor
○ **PAR-1 antagonists** Vorapaxar	
○ **PDE inhibitors** Cilostazol	
○ **PDE and adenosine reuptake inhibitors** Dipyridamole	

*Some antiplatelt agents are also available as fixed-dose combinations
Abbreviations: COX, cyclooxygenase; GP, glycoprotein; PAR, protease-activated receptor-1; PDE, phosphodiesterase

Appendix B

Literature Search for Systematic Reviews

Table 1. Medline Literature Search Strategy for SRs (2010-current)

1) Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R). Search Strategy Date: **10-20-2017**
1 (cangrelor or "ar c69931 mx" or "ar c69931 xx" or "ar c69931mx" or "ar c69931xx" or Kengreal).ti,ab,kw,kf,rn. (510)
2 (clopidogrel* or clopilet* or grepid* or iscover* or "pcr 4099" or pcr4099 or Plavix* or "sr 25989" or "SC 25989C" or "sr 25990c" or sr25989 or sr25990c or zopya* or zylagren* or zyllt*).ti,ab,kw,kf,rn. (13117)
3 Prasugrel Hydrochloride/ or (prasugrel* or "cs 747" or cs747 or effient* or efient* or "ly 640315" or ly640315).ti,ab,kw,kf,rn. (2054)
4 (ticagrelor* or "azd 6140" or azd6140 or brilinta* or brilique* or possia*).ti,ab,kw,kf,rn. (1973)
5 Ticlopidine/ or (ticlopidin* or agulan* or anagregal* or antigreg* or aplaket* or cartrilet* or cenpidin* or clotidon* or crodin* or declot* or deistic* or goclid* or licodin* or nufaclapid* or panaldin* or siclot* or tacron* or ticard* or ticdin* or ticlid* or ticlidil* or ticlodin* or ticlodix* or ticlodon* or ticlomed* or ticlon* or ticuring* or tikleen* or tiklid* or tiklyd* or tikol* or tiloden* or tiodin* or tipidin* or tipidin* or tyklid* or viladil* or "53 32C" or 5332C).ti,ab,kw,kf,rn. (11330)
6 (vorapaxar or "sch 530348" or sch530348 or zontivit*).ti,ab,kw,kf,rn. (308)
7 1 or 2 or 3 or 4 or 5 or 6 [all drugs] (16985)
8 Platelet Aggregation Inhibitors/ [drug class] (33931)
9 exp animals/ not humans.sh. (4679925)
10 (animal? or beaver? or beef or bovine or breeding or bull or canine or castoris or cat or cattle or cats or chicken? or chimp$ or cow or dog or dogs or equine or foal or foals or fish or insect? horse or horses or livestock or mice or monkey? or mouse or murine or plant or plants or pork or porcine or protozoa? or purebred or rat or rats or rodent? or sheep or thoroughbred).ti. or veterinar$.ti,ab,kw,kf,hw. (2277194)
11 9 or 10 [all animal] (5187317)
12 ((systematic adj2 review) or (overview adj3 review?)).ti. or (metaanaly$ or meta-analy$).ti,ab,pt. or ((systematic adj2 review) or (metaanaly$ or meta-analy$)).kw,kf. (197491)
13 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. (1212424)
14 7 not 11 (16187)
15 limit 14 to english language (14280)
16 15 and 12 [SR - drugs] (528)
17 (15 and 13) not 16 [RCT- drugs] (3478)
18 8 not 11 (30528)
19 limit 18 to english language (26577)
20 (19 and 12) not 16 [SR - drug class not drug] (599)
21 (19 and 13) not 17 [RCT - drug class not drugs] (3803)
22 16 or 20 [SRs = drugs + drug class] (1127)
23 remove duplicates from 22 [ALL SRs = drugs + drug class] (1005)
24 17 or 21 [RCT = drug or drug class] (7281)
25 24 not 22 [all RCTs NOT all SRs] (6732)
26 limit 23 to yr="2010 -Current" [ALL SRs = drugs + drug class| from 2010 -present] (673)
27 25 (6732)
28 limit 27 to yr="**2010 -Current**" (3030)
29 remove duplicates from 28 [All RCTs not SRs | 2010 - present] (2648)

Table 1. Medline Literature Search Strategy for SRs (2010-current)

2) Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R). Search Strategy Date: **11/29/17** (Search for **aspirin/dipyridamole**)
1 Aspirin, Dipyridamole Drug Combination/ or ('acetylsalicylic acid plus dipyridamole' or aggrenox or asasantin or 'asasantin retard' or 'asasantin sr' or 'asasantine lp' or 'aspirin plus dipyridamole' or 'aspirin, dipyridamole drug combination' or 'dipyridamole plus acetylsalicylic acid' or 'dipyridamole plus aspirin').ti,ab,kw,kf,rn. (243)
2 (('salicylic acid' or 'acetylsalicylic acid' or aspirin) adj3 dipyridamole).ti,ab,kw,kf,rn. (2257)
3 1 or 2 (2271)
4 (((systematic adj2 review) or (overview adj3 review?)).ti. or (metaanaly$ or meta-analy$).ti,ab,pt. or ((systematic adj2 review) or (metaanaly$ or meta-analy$)).kw,kf.) not ((exp animals/ not humans.sh.) or (animal? or beaver? or beef or bovine or breeding or bull or canine or castoris or cat or cattle or cats or chicken? or chimp$ or cow or dog or dogs or equine or foal or foals or fish or insect? horse or horses or livestock or mice or monkey? or mouse or murine or plant or plants or pork or porcine or protozoa? or purebred or rat or rats or rodent? or sheep or thoroughbred).ti. or veterinar$.ti,ab,kw,kf,hw.) (199872)
5 3 and 4 (89)
6 limit 5 to (english language and yr="**2010 -Current**") (33)
7 remove duplicates from 6 (29)

Table 2. Embase Literature Search Strategy for SRs (2010-current)

1) EMBASE.com. Search Strategy Date: **10-20-2017**

No.	Query	Results
#29	#27 AND [2010-2018]/py	2,046
#28	#26 AND [2010-2018]/py	575
#27	#25 OR #18	3,404
#26	#16 OR #23	878
#25	#24 NOT #23	446
#24	#22 AND #12	499
#23	#22 AND #11	219
#22	#21 NOT #15	4,776
#21	#20 NOT #10	6,580
#20	#19 NOT #9	7,309
#19	#8 AND [english]/lim	8,341
#18	#17 NOT #16	2,958
#17	#15 AND #12	3,124
#16	#15 AND #11	659
#15	#14 NOT #10	16,086
#14	#13 NOT #9	16,916
#13	#7 AND [english]/lim	25,710
#12	'clinical study'/mj OR 'clinicaltrial'/mj OR 'controlled clinical trial'/mj OR 'controlled study'/mj OR 'major clinical study'/mj OR controlled OR multicentre OR multicenter OR 'multi centre' OR 'multi center') NEAR/3 (study OR trial)):ab) OR placebo:ab,ti OR	2,579,833
#11	'meta analysis'/mj OR 'systematic review'/de OR (((systematic OR integrative OR drug OR therapeutic*) NEAR/2 review):ti) OR 'meta	254,264
#10	('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de))	6,326,088
#9	'conference abstract'/it OR 'conference paper'/it	3,486,388
#8	'antithrombocytic agent'/mj OR 'thrombin receptor antagonist'/mj	10,620
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6	29,178
#6	'vorapaxar'/de OR vorapaxar:ti,ab,dn,mn,m,tn OR 'sch 530348':ti,ab,dn,mn,m,tn OR sch 530348:ti,ab,dn,mn,m,tn OR	811
#5	'ticlopidine'/mj OR ticlopidin*:ti,ab,dn,mn,m,tn OR aguian*:ti,ab,dn,mn,m,tn OR anagregal*:ti,ab,dn,mn,m,tn OR clotidon*:ti,ab,dn,mn,m,tn OR crodin*:ti,ab,dn,mn,m,tn OR declot*:ti,ab,dn,mn,m,tn OR delstic*:ti,ab,dn,mn,m,tn OR siclot*:ti,ab,dn,mn,m,tn OR tacron*:ti,ab,dn,mn,m,tn OR ticard*:ti,ab,dn,mn,m,tn OR ticlin*:ti,ab,dn,mn,m,tn OR ticlid*:ti,ab,dn,mn,m,tn ticlomed*:ti,ab,dn,mn,m,tn OR ticlon*:ti,ab,dn,mn,m,tn OR ticuring*:ti,ab,dn,mn,m,tn OR tiklean*:ti,ab,dn,mn,m,tn OR OR tiplidin*:ti,ab,dn,mn,m,tn OR tyklid*:ti,ab,dn,mn,m,tn OR viladil*:ti,ab,dn,mn,m,tn OR '53 32c':ti,ab,dn,mn,m,tn OR	5,770
#4	'ticagrelor'/mj OR ticagrelor*:ti,ab,dn,mn,m,tn OR 'azd 6140':ti,ab,dn,mn,m,tn OR azd6140:ti,ab,dn,mn,m,tn OR	3,415
#3	'prasugrel'/mj OR prasugrel*:ti,ab,dn,mn,m,tn OR 'cs 747':ti,ab,dn,mn,m,tn OR cs747:ti,ab,dn,mn,m,tn OR effient*:ti,ab,dn,mn,m,tn OR	3,526
#2	'clopidogrel'/mj OR clopidogrel*:ti,ab,dn,mn,m,tn OR clopilet*:ti,ab,dn,mn,m,tn OR grepid*:ti,ab,dn,mn,m,tn OR 25989':ti,ab,dn,mn,m,tn OR 'se 25989e':ti,ab,dn,mn,m,tn OR 'sr 25990e':ti,ab,dn,mn,m,tn OR sr25989:ti,ab,dn,mn,m,tn OR	22,761
#1	'cangrelor'/de OR cangrelor*:ti,ab,dn,mn,m,tn OR 'arc69931mx':ti,ab,dn,mn,m,tn OR 'arc69931xx':ti,ab,dn,mn,m,tn OR 'ar	1,313

2) EMBASE.com. Search Strategy Date: **11/29/17** (Search for **aspirin/dipyridamole**)

#6	#3 AND #4 AND [2010-2017]/py	**42**
#5	#3 AND #4	100
#4		194,784

('meta analysis'/mj OR 'systematic review'/de OR (((systematic OR integrative OR drug OR therapeutic*) NEAR/2 review):ti) OR 'meta analys*':ti,ab OR metaanaly*:ti,ab) NOT ('conference abstract'/it OR 'conference

Table 2. Embase Literature Search Strategy for SRs (2010-current)	
paper'/it OR (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell'/de)))) AND [english]/lim	
#3 #1 OR #	2 2,193
#2 (('salicylic acid' OR 'acetylsalicylic acid' OR aspirin) NEAR/3 dipyridamole):ti,ab,dn,mn,rn,tn	1,422
#1	1,049
'acetylsalicylic acid plus dipyridamole'/de OR aggrenox:ti,ab,dn,mn,rn,tn OR asasantin:ti,ab,dn,mn,rn,tn OR 'asasantin retard':ti,ab,dn,mn,rn,tn OR 'asasantin sr':ti,ab,dn,mn,rn,tn OR 'asasantine lp':ti,ab,dn,mn,rn,tn OR 'aspirin plus dipyridamole':ti,ab,dn,mn,rn,tn OR 'aspirin, dipyridamole drug combination':ti,ab,dn,mn,rn,tn OR 'dipyridamole plus acetylsalicylic acid':ti,ab,dn,mn,rn,tn OR 'dipyridamole plus aspirin':ti,ab,dn,mn,rn,tn	

Literature Search for Randomized Controlled Trials

Table 3. Medline Literature Search Strategy for RCTs (excluding cangrelor) [2015-current]
Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R). Search Strategy Date: **12-05-2017**
1 **Aspirin, Dipyridamole** Drug Combination/ or ('acetylsalicylic acid plus dipyridamole' or aggrenox or asasantin or 'asasantin retard' or 'asasantin sr' or 'asasantine lp' or 'aspirin plus dipyridamole' or 'aspirin, dipyridamole drug combination' or 'dipyridamole plus acetylsalicylic acid' or 'dipyridamole plus aspirin').ti,ab,kw,kf,rn. or (('salicylic acid' or 'acetylsalicylic acid' or aspirin) adj3 dipyridamole).ti,ab,kw,kf,rn. (2271)
2 (**clopidogrel*** or clopilet* or grepid* or iscover* or "pcr 4099" or pcr4099 or Plavix* or "sr 25989" or "SC 25989C" or "sr 25990c" or sr25989 or sr25990c or zopya* or zylagren* or zyllt*).ti,ab,kw,kf,rn. (13336)
3 **Prasugrel** Hydrochloride/ or (prasugrel* or "cs 747" or cs747 or effient* or efient* or "ly 640315" or ly640315).ti,ab,kw,kf,rn. (2098)
4 (**ticagrelor*** or "azd 6140" or azd6140 or brilinta* or brilique* or possia*).ti,ab,kw,kf,rn. (2040)
5 **Ticlopidine**/ or (ticlopidin* or agulan* or anagregal* or antigreg* or aplaket* or cartrilet* or cenpidin* or clotidon* or crodin* or declot* or deistic* or goclid* or licodin* or nufaclapid* or panaldin* or siclot* or tacron* or ticard* or ticdin* or ticlid* or ticlidil* or ticlodin* or ticlodix* or ticlodon* or ticlomed* or ticlon* or ticuring* or tikleen* or tiklid* or tiklyd* or tikol* or tiloden* or tiodin* or tipidin* or tipidin* or tyklid* or viladil* or "53 32C" or 5332C).ti,ab,kw,kf,rn. (11489)
6 (**vorapaxar** or "sch 530348" or sch530348 or zontivit*).ti,ab,kw,kf,rn. (311)
7 1 or 2 or 3 or 4 or 5 or 6 [all drugs] (18824)
8 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not ((exp animals/ not humans.sh.) or (animal? or beaver? or beef or bovine or breeding or bull or canine or castoris or cat or cattle or cats or chicken? or chimp$ or cow or dog or dogs or equine or foal or foals or fish or insect? horse or horses or livestock or mice or monkey? or mouse or murine or plant or plants or pork or porcine or protozoa? or purebred or rat or rats or rodent? or sheep or thoroughbred).ti. or veterinar$.ti,ab,kw,kf,hw.) (1123366)
9 7 and 8 (4637)
10 limit 9 to (english language and yr="2015 -Current") (946)
11 remove duplicates from 10 **(771)**

Table 4. Embase Literature Search Strategy for RCTs (excluding cangrelor) [2015-current]

Embase.com. Search Strategy Date: **12-05-2017**

No.	Query	Results
#9	#7 AND #8 AND [2015-2017] /py	802
#8	('clinical study' /m j OR 'clinical trial'/mj OR 'controlled clinical trial' /mj OR 'controlled study'/mj OR 'major clinical study'/mj OR 'randomized controlled trial'/mj OR 'control group'/mj OR (((clinical OR comparative OR efficacy OR effectiveness OR randomi* OR controlled OR multicentre OR multicenter OR 'multi centre' OR 'multi center') NEAR/3 (study OR tri al)):a b) OR pl acebo:ab,ti OR controlled:ti OR trial:ti OR multicent*:ti OR 'multi cent*':ti OR study:ti OR randomly:ab OR 'head to head':ti,ab) NOT ('conference abstract '/it OR 'conference paper'/it OR (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell' /exp OR 'nonhuman'/de) NOT (('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/e xp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell' /exp OR 'nonhuman'/de) AND ('human'/exp OR 'human cell' /de)))) AND [english]/lim	1,511,645
#7	**#1** OR **#2** OR **#3** OR **#4** OR **#5** OR **#6**	29,178
#6	**'vorapaxar' /de** OR vorapaxar:ti,ab,dn,mn,rn,tn OR **'sch** 530348':ti,ab,dn, mn,rn,tn OR sch530348:ti,ab,dn, mn,rn,tn OR zontivit* :ti,ab,dn,m n,rn,tn	811
#5	**'ticlopidine'/mj** OR ticlopidin*:ti ,ab,d n,mn,rn,t n OR agulan*:ti ,ab,dn,mn,rn,tn OR anagregal*:ti,ab ,dn,mn,rn,tn OR antigreg*:ti ,ab,dn,mn,rn,tn OR aplaket*:ti ,ab,dn,mn,rn,tn OR cartrilet*:ti ,ab,dn,mn,rn,tn OR cenpidin* :ti,ab,dn,mn, rn,tn OR clotidon*: ti,ab,dn,mn, rn,tn OR crodin*:ti,ab,dn,mn,rn,tn OR declot*: ti,ab,dn,mn, rn,tn OR deistic*:ti,ab ,dn, mn,rn,tn OR goc li d*:ti ,ab,dn,mn,rn,tn OR li codin* :ti,ab,dn,mn,rn,tn OR nuf aclapid*:ti ,ab,dn,mn,rn,tn OR p analdin* :ti,ab,dn,mn,rn,tn OR siclot*:ti ,ab,dn,mn,rn,t n OR t acron*:ti ,ab,dn,mn, rn,tn OR ti card*:ti ,ab,dn,mn,rn,tn OR ti cdin*:ti ,ab,dn,mn, rn,t n OR ticlid*:ti ,ab,dn,mn,rn,tn OR ticlidil* :t i,ab,dn,mn,rn,tn OR ticlodin*:ti ,ab,dn,mn,rn,tn OR ticlodix*:ti ,ab,dn,mn,rn,tn OR ticlodon* :ti,ab,dn,mn, rn,tn OR ticlomed*:ti,ab ,dn, mn,rn,tn OR ticlon*:ti,ab,dn,mn,rn,tn OR ticuring*:ti,ab,dn,mn,rn,tn OR tikle en*:ti, ab,dn,m n,rn,tn OR tiklid*:ti,ab,dn,mn,rn,tn OR tiklyd* :t i,ab,dn,mn, rn,tn OR tikol*:t i,ab, dn,mn,rn,tn OR tiloden*:ti,ab,dn,mn,rn,tn OR tiodin*:ti ,ab,dn, mn,rn,tn OR tipidin*:ti, ab,dn,mn,rn ,tn OR tyklid*:ti ,ab,d n,mn, rn,tn OR vil adil *:ti,ab,dn,mn,rn,tn OR **'53** 32c':ti,ab ,dn,mn ,rn,tn OR 5332c:ti,ab,dn,mn, rn,tn	5,770
#4	**'ticagrelor'/mj** OR ti cagrelor*:t i,ab,dn,mn,rn,tn OR **'azd** 6140':ti,ab,dn, mn,rn,tn OR azd6140:ti,ab,dn,mn,rn,tnOR brilint a* :ti,ab,dn,mn,rn,tn OR brilique*:ti,ab ,dn, mn,rn,tn OR po ssia*:ti,ab,dn,mn,rn,tn	3,415
#3	**'prasugrel' /mj** OR pr asugrel*:ti ,ab,dn,mn, rn,tn OR **'cs** 747':ti,ab,dn,mn,rn,tn OR cs747:ti,ab,dn, mn,rn,tn OR effi ent*:ti,ab,dn, mn,rn,tn OR efi ent* :ti,ab,dn, mn,rn,tn OR **'ly** 640315':ti,ab,dn, mn,rn,tn OR ly640315:ti,ab,dn,mn,rn,tn	3,526
#2	**'clopidogrel'/mj** OR clopidogrel* :ti,ab,dn, mn,rn,tn OR clopilet*:t i,ab,dn, mn,rn,tn OR gr epid* :ti,ab,dn,mn,rn,tn OR iscover*:ti,ab,dn,mn,rn,tn OR **'per** 4099':ti,ab,dn,m n,rn ,tn OR pcr 4099:ti,ab,dn, mn ,rn,tn OR pl avix*:ti ,ab,dn,mn,rn,tn OR **'sr** 25989':ti,ab,dn,mn,rn,tnOR **'sc** 25989c':ti,ab,dn,mn,rn,tn OR **'sr** 25990c' :ti,ab,dn,mn, rn,tn OR sr25989:ti,ab,dn, mn,rn,tn OR sr25990c:ti,ab ,dn,mn,rn,tn OR zopya*:ti,ab ,dn,mn,rn,tn OR zylagren*:ti,ab ,dn,mn,rn,tn OR zyllt* :ti,ab,dn,mn,rn,tn	22,761
#1	**'acetylsalicylic acid plus dipyridamole'/de** OR aggrenox:ti, ab,dn,mn,rn,tn OR asasantin :ti,ab,dn,mn,rn,tn OR **'asasantin** retard ':ti,ab,dn,mn,rn,tn OR **'asasantin** sr':ti,ab,dn,mn,rn,tn OR **'asasantine** lp' :ti,ab,dn,mn,rn,tn OR **'aspirin plus** dipyridamole':ti,ab ,dn,mn,rn,tn OR **'aspirin, dipyridamole drug** combination' :ti,ab,dn,mn,rn,tn OR **'dipyridamole plus acetylsalicylic** acid':ti,ab,dn,mn,rn,tn OR **'dipyridamole plus** aspirin':ti ,ab,dn,mn, rn,tn OR **(((salicylic acid'** OR **'acetylsalicylic acid'** OR **aspirin)** NEAR/3 dipyridamole):ti ,ab,dn,mn,rn,tn)	2,193

Appendix C

Table 1. Characteristics of Included Systematic Reviews/Meta-Analyses

	Study Title	Author, year	Type of Study	Population	Drugs	Number of Studies	Literature Search Databases	Literature Search Date	Efficacy Endpoints	Safety Endpoints
1	Head-to-head comparison of prasugrel versus ticagrelor in patients undergoing percutaneous coronary intervention: A meta-analysis of randomized controlled trials	Sakurai 2017	MA of RCTs	PCI	Tica, pra	12	PubMed, the Cochrane Library, and Web of Science	Feb-2017	Death, MI, stroke, and ST	Bleeding
2	Comparison of prasugrel and ticagrelor in patients with acute coronary syndrome undergoing percutaneous coronary intervention: A meta-analysis of randomized and non-randomized studies	Watti 2017	MA of RCT and non-RCT	ACS with PCI	Pra, tica	9	PUBMED, EMBASE, Cochrane CENTRAL, CINAHL and manual search	Nov-16	Mortality, MI, stroke, revascularization, ST	BARC bleeding ≥ 2
3	Comparison of Treatment Outcomes of	Yang 2017	MA of RCTs	PCI	Clo, tica	6	MEDLINE database, Cochrane	2015	All-cause mortality, MI, stroke	Total bleeding, and minor or major

	Ticagrelor and Clopidogrel among Patients Undergoing Percutaneous Coronary Intervention: A Meta-analysis*						library, and EMBASE database.			bleeding
4	The clinical efficacy and safety evaluation of ticagrelor for acute coronary syndrome in general ACS patients and diabetic patients: A systematic review and meta-analysis	Tan 2017	MA of RCTs and retrospective studies	ACS and diabetic patients	Clo, pra, tica	22	PubMed, Cochrane Central Register of Controlled Trials, Web of Science, CNKI databases	2015	Composite endpoint (containing the probability of any MI, cardiovascular death or stroke).	Bleeding events and dyspnea
5	Cancer Event Rate and Mortality with Thienopyridine: A Systematic Review and Meta-Analysis	Kotronias 2017	MA of RCTs	Patients with and without exposure to thienopyridines.	Ticlo, pra, clo, tica	9	MEDLINE and EMBASE databases	Feb-16	Not reported	Incident cancer and cancer mortality
6	Comparison of new adenosine diphosphate receptor antagonists with clopidogrel in patients with coronary artery	Bae 2016	MA of RCTs	CAD patients undergoing PCI	Clo, Pra, tica, can	9	MEDLINE, EMBASE, and Cochrane databases	Feb-14	Primary efficacy endpoint: composite end point of all-cause mortality, nonfatal MI, or non-fatal stroke.	Rate of major bleeding defined according to the TIMI group, and not related to CABG, at the longest available follow-up

	disease: a meta-analysis									
7	P2Y12 receptor antagonists: Which one to choose? A systematic review and meta-analysis	Briasoulis 2016	MA of RCTs	ACS and/or PCI	Clo, tica, pra	11	MEDLINE, EMBASE, CENTRAL	Nov-15	Primary outcomes: MACE, all-cause mortality, MI, stroke, and stent thrombosis	Major bleeding
8	Meta-Analysis of Comparison of the Newer Oral P2Y12 Inhibitors (Prasugrel or Ticagrelor) to Clopidogrel in Patients with Non-ST-Elevation Acute Coronary Syndrome	Bavishi 2015	MA of RCTs	NSTE-ACS	Clo, para, tica	4	PUBMED, EMBASE, CINAHL, Web of Science, ClinicalTrials. gov, and Google Scholar. Manual searches through the reference lists of studies, reviews, and pertinent meta-analysis on this topic	Feb-15	Composite end point of cardiovascular death, myocardial infarction (MI), and stroke.	bleeding events
9	Meta-Analysis of Randomized Controlled Trials Comparing Risk of Major Adverse Cardiac Events and Bleeding in Patients With Prasugrel Versus Clopidogrel	Chen 2015	MA of RCTs	CAD	Clo, pra	9	PubMed, EMBASE, and Cochrane Central Register of Controlled Trial databases	Nov-2014	Combined rates of MACEs, and bleeding	

10	Efficacy of Antiplatelet Therapy in Secondary Prevention Following Lacunar Stroke: Pooled Analysis of Randomized Trials	Kwok 2015	MA of RCTs	Secondary prevention after acute stroke (Lacunar stroke)	Clo, tica, ticlo, dipyrida mole	17	MEDLINE and Embase. we reviewed the bibliography of included trials, Cochrane Reviews, and the most recent review by the antithrombot ic trialist collaboration for additional studies	Dec-13	Reduction in recurrence of any stroke and ischemic stroke	
11	Efficacy and safety of cangrelor for patients with coronary artery disease: A meta-analysis of four randomized trials	Tang 2015	MA of RCTs	CAD	Can , clo	4	PubMed, Web of Science, Embase, and Cochrane Database searches	Mar-14	MACE	Major or severe bleeding at 48 hours
12	Dyspnea and reversibility profile of P2Y12 antagonists: Systematic review of new antiplatelet drugs	Caldeira 2014	MA of RCTs		Clo, para, tica, can	8	MEDLINE/Pu bMed, CENTRAL, and ISI Web of Knowledge	Mar-13	Not reported	Dyspnea
13	Cangrelor versus clopidogrel in percutaneous coronary intervention: A	Pandit 2014	MA of RCTs	ACS (STEMI, NSTEMI/UA)	Can, clo	3	EMBASE, PubMed, CINAHL, Cochrane and	May-13	Primary endpoint: composite of death, IDR, and MI at 48 hours. Stent thrombosis.	GUSTO severe or life-threateningblee ding

	systematic review and meta-analysis						Web of Knowledge		Secondary endpoints: all-cause mortality, IDR, MI	
14	Cangrelor for patients undergoing percutaneous coronary intervention: Evidence from a meta-analysis of randomized trials	Sardar 2014	MA of RCTs	Patients undergoing PCI	Can, clo	3			Risk of MI	TIMI major bleeding at 48 h
15	Benefits from new ADP antagonists as compared with clopidogrel in patients with stable angina or acute coronary syndrome undergoing invasive management: A meta-analysis of randomized trials	Verdoia 2014	MA of RCTs	patients with acute coronary syndromes or stable angina	Clo, pra, tica	8	Pubmed, EMBASE, Cochrane and main scientific sessions abstracts	Apr-13	Primary endpoint was mortality. Secondary endpoints were: (1) nonfatal myocardial infarction (MI), (2) recurrent ischemia symptoms or ischemia-driven revascularization (RI/IDR), (3) ST	Secondary endpoints: safety endpoints, defined as for TIMI Major Bleeding criteria
16	Antiplatelet Treatment for Prevention of Cerebrovascular Events in Patients With Vascular Diseases	Gouya 2014	MA of RCTs	Patients with CV disease, with and without any previous cerebro-vascular event		22	Pubmed, EMBASE, Cochrane, Web of Science	3rd quarter 2011	Total stroke, ischemic stroke or TIA	Intracranial hemorrhage

17	A meta-analysis of haemorrhage with ticlopidine and clopidogrel following coronary artery stent placement	Ronaldson 2012	MA RCT/ non-RCT	Patients undergoing coronrary artery stenting	Clo, ticlo	7 RCTs + 5 non-RCTs	Medline, Embase and the Cochrane	Dec-10	Not reported	Hemorrhage

Abbreviations: ACS, Acute Coronary Syndrome; CAD, coronary artery disease; can, cangrelor; clo, clopidogrel; DAPT, dual antiplatelet therapy; MA, meta-analysis; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; pra, prasugrel; RCT, randomized controlled trial; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic stroke; tica, ticagrelor; ticlo, ticlopidine; UA, unstable angina

Appendix D

Table 1. Results Reported in Systematic Reviews/Meta-Analyses

	Study/Country first author	RESULTS (*Abstract*)
1	Sakurai 2017	*"The risks of death (odds ratio [OR]: 0.86, 95% confidence interval [CI]: 0.46-1.62, P = 0.647), MI (OR: 1.61, 95%CI: 0.71-3.62, P = 0.252), stroke (OR: 1.45, 95%CI: 0.25-8.36, P = 0.680), and ST (OR: 0.76, 95%CI: 0.20-2.81, P = 0.677) were similar between prasugrel and ticagrelor, respectively. While the incidence of bleeding according to the Bleeding Academic Research Consortium definitions was also comparable (OR: 0.83, 95%CI: 0.45-1.52, P = 0.539), that according to the Thrombolysis in Myocardial Infarction criteria was lower in prasugrel than ticagrelor (OR: 0.49, 95%CI: 0.24-0.97, P = 0.042).* ***Conclusions****: Although the efficacy was similar between prasugrel and ticagrelor, prasugrel may be associated with a lower risk of bleeding compared with ticagrelor during short- to mid-term follow-up period after PCI. Further studies are warranted in a larger patient population during longer-term follow up to validate these findings."*
2	Watti 2017	***"Results****: A total of 9 studies with 21,360 total patientswere included in the meta-analysis. Compared to ticagrelor, prasugrel was associated with lower rate of MI [0.8% vs. 1.9%; 0.54 (0.29–0.99); P = 0.05] but no difference was noted in mortality [2.1% vs. 2.4%; 0.84 (0.64–1.09); P = 0.19], repeat revascularization [1.6% vs. 2.1%; 0.82 (0.61–1.10); P = 0.19] and stroke [0.2% vs. 0.3%; 0.68 (0.25–1.83); P = 0.44] between two agents. In addition, prasugrel was associated with lower risk of BARC ≥2 bleeding [2.5% vs. 3.8%; 0.75 (0.59–0.95); P = 0.02] and showed a trend toward a lower risk of ST [0.3% vs. 0.6%; 0.55 (0.28–1.07); P = 0.08] in comparison with ticagrelor.* ***Conclusions****: Based on thismeta-analysis of observational and randomized studies, prasugrel appears to be equivalent or superior to ticagrelor in patients with ACS undergoing PCI on the 30-day follow up. Larger randomized trials with longer follow-ups are needed to establish superiority of one agent over the other."*
3	Yang 2017	*"There was a significant decrease of all-cause mortality (MD=0.83, 95%CI=0.74–0.93, P=0.001) and myocardial infarction (MI) (MD=0.78, 95%CI=0.70–0.88, P=0.000). There were no significant differences in stroke (MD=1.34, 95%CI=0.99–1.79, P=0.06), total bleeding (MD=0.97, 95%CI=0.84–1.12, P=0.66), minor or major bleeding (MD=1.06, 95%CI=0.94–1.19, P=0.35) in patients undergoing PCI after treatment with TIC vs. CLO. TIC could be more significant in decreasing all-cause mortality and MI than CLO, but there were no significant differences between TIC and CLO in inhibiting stroke, major bleeding, major or minor bleeding in patients undergoing PCI."*
4	Tan 2017	*"The meta-analysis result implicated that ticagrelor could: 1) reduce the incidence of the composite endpoint [OR = 0.83, 95%CI (0.77, 0.90), P<0.00001] and the incidence of myocardial infarction [OR = 0.81, 95% CI (0.74, 0.89), P = 0.0001]; 2) not statistically reduce the incidence of cardiovascular death, the incidence of stroke and the incidence of bleeding events; 3) increase the incidence of dyspnea [OR = 1.90, 95%CI (1.73, 2.08), P<0.00001] compared with clopidogrel. Meanwhile, compared with prasugrel, ticagrelor could 1) reduce the platelet reactivity of patients at maintenance dose [MD = -44.59, 95%CI (-59.16, -30.02), P<0.00001]; 2) not statistically reduce the incidence of cardiovascular death, the platelet reactivity of patients 6 hours or 8 hours after administration, or the incidence of bleeding events; 3) induce the incidence of dyspnea [OR = 13.99, 95%CI (2.58, 75.92), P = 0.002]. Furthermore, the result of metaregression analysis implicated that there was a positive correlation between DM patients and the platelet reactivity of*

	Study/Country first author	RESULTS (*Abstract*)
		patients 6 hours and 8 hours after administration, but there was no obvious correlation between DM patients and general ACS patients in other endpoints ***Conclsuion**: Ticagrelor could reduce the incidence of composite endpoint of cardiovascular death, myocardial infarction and stroke as well as platelet reactivity in DM patients with ACS, while not increasing the risk of bleeding. Because there are differences in platelet reactivity between DM patients and general ACS patients, we suggest that caution is needed when using ticagrelor in clinical applications."*
5	Kotronias 2017	*"The cancer event rate with clopidogrel and prasugrel was 3.25% and 1.58% respectively. When compared with standard aspirin or placebo, thienopyridines are not significantly associated with cancer mortality and event rate (odds ratio [OR] 1.12, 95% confidence interval [CI] 0.80–1.56, n = 3; and OR 0.92, 95% CI 0.52–1.64, n = 2, respectively. Further analyses examining clopidogrel showed no significant association with cancer event rate or malignancy-related death. When comparing prasugrel with clopidogrel, no significant association was noted for cancer event rate (OR 1.10, 95% CI 0.89–1.37, n = 2]* ***Conclusions** Our results suggest that there is currently insufficient evidence to suggest that thienopyridine exposure is associated with an increased risk of cancer event rate or mortality."*
6	Bae 2016	*"New ADP receptor antagonists reduced the composite incidence of all-cause mortality, myocardial infarction or stroke (odds ratio [OR] 0.89, 95 % confidence interval [CI] 0.81–0.97, p = 0.01) but increased the incidence of non-coronary artery bypass grafting-related major bleeding (OR 1.24, 95 % CI 1.08–1.42, p = 0.003). The composite end point of the net rate of adverse clinical events, which was the combination of the primary efficacy end point and the primary safety end point, was significantly lower in the new agent group compared to the clopidogrel group (9.7 versus 10.6 %, OR 0.92, 95 % CI 0.85–1.00). Use of recently introduced new ADP receptor antagonists results in a reduction in adverse clinical outcomes but a substantial increase in bleeding. New agents revealed an improved combined efficacy and safety outcome compared to that of clopidogrel in patients with CAD.* *<u>Article</u>* *The use of new ADP receptor antagonists, as compared with clopidogrel was associated with an 11 % reduction in the rate of **composite end points** (**all-cause mortality, MI, or stoke**) and a 43 % reduced risk of **stent thrombosis**. However, there was an approximately 24 % increased risk for **major bleeding** not related to CABG in the new ADP receptor antagonists group compared to that of the clopidogrel group.* *<u>Sensitivity Analysis</u>* *The sensitivity analysis by study agents yielded **significantly lower rates of the risk of composite endpoint in studies comparing prasugrel or ticagrelor with clopidogrel, whereas no beneficial effect was seen in studies using intravenous cangrelor** or elinogrel as the comparator.* *The sensitivity analysis of **non-CABG-related major bleeding** by study agents yielded significantly higher incidence of bleeding in studies comparing prasugrel or ticagrelor with clopidogrel, whereas no differences were observed in studies comparing cangrelor or elinogrel with clopidogrel."*
7	Briasoulis 2016	*"Ticagrelor use was associated with significantly reduced MACE, all-cause mortality, myocardial infarction and stent thrombosis and similar rates of stroke and major bleeding compared to clopidogrel in patients with ACS and/or PCI.* *Prasugrel use was associated with significantly lower rates of MACE, MI and stent thrombosis but significantly high rates of major bleeding and thus no all-cause mortality benefit compared to clopidogrel.*

	Study/Country first author	RESULTS (*Abstract*)
		***Conclusion**: Newer P2Y12 receptor antagonists are associated with better cardiovascular outcomes in patients with ACS and/or undergoing PCI. Prasugrel use resulted in higher major bleeding rates and no overall mortality benefit compared with clopidogrel."*
8	Bavishi 2015	*"Newer oral P2Y12 inhibitors significantly decreased MACE (relative risk [RR] 0.87, 95% confidence interval [CI] 0.80 to 0.95) and MI (RR 0.85, 95% CI 0.75 to 0.96) and showed a trend toward reduction of cardiovascular death (RR 0.89, 95% CI 0.71 to 1.01). There was a significant increase in TIMI major bleeding (RR 1.27, 95% CI 1.07 to 1.50) and TIMI major or minor bleeding (RR 1.20, 95% CI 1.02 to 1.42). Results were largely similar when stratified by ticagrelor versus prasugrel (pinteraction >0.05) except for increased TIMI major/minor bleeding with prasugrel than ticagrelor (p interaction [0.01). In conclusion, in patients with NSTE-ACS, newer oral P2Y12 inhibitors decrease MACE and MI at the expense of a significant increase in the risk of bleeding. Treatment of 1,000 patients with newer oral P2Y12 inhibitors will prevent 16 MACE and 13 MIs at the expense of increase in 6 major bleeding events."*
9	Chen 2015	*"Nine studies involving 25,214 patients were included in our meta-analysis. In both the random- and fixed-effects models, the risks of MACEs outweighed those of major bleeding (OR 7.48, 95% CI 3.75 to 14.94, p <0.0001, random effects) and of minor bleeding (OR 3.77, 95% CI 1.73 to 8.22, p [0.009, random effects). Results were corroborated in a standard-dose clopidogrel subgroup analysis (OR 7.46, 95% CI 3.54 to 15.68, p <0.0001, and OR 6.44, 95% CI 2.80 to 14.80, p <0.0001, random effects, respectively). In conclusion, despite the increased risk of bleeding associated with prasugrel treatment compared with clopidogrel, the risk of MACEs far outweighed the risk of bleeding."*
10	Kwok 2015	*"We observed no significant advantage of **DAPT versus clopidogrel** or **ticlopidine versus clopidogrel**. For this analysis, **aspirin/ dipyridamole** did not seem to be superior to **clopidogrel** alone. Finally, DAPT using vorapaxar in addition to aspirin or clopidogrel use showed no significant benefit on vascular end points (HR 0.99,0.75–1.31).* ***Conclusion**:* *Dual antiplatelet therapy should not be used for long-term stroke prevention in this stroke subtype."*
11	Tang 2015	***"**<u>Abstract</u>:* *Cangrelor significantly decreased risk of MACE (OR: 0.87, P = 0.002) and stent thrombosis (OR: 0.53, P < 0.001). However, at the same time, an increase in TIMI minor bleeding (OR: 1.49, P = 0.04) and in GUSTO moderate bleeding (OR: 1.43, P = 0.04) were observed by cangrelor. **Conclusions**: Intravenous administration of cangrelor is benefit to reduce risk of MACE and stent thrombosis in patients with CAD excepting for increased minor bleeding events."*
12	Caldeira 2014	***"Conclusion**: The reversible P2Y12 antagonists ticagrelor, cangrelor, and elinogrel have an increased incidence of dyspnea in increasing order when compared with irreversible P2Y12 inhibitors such as clopidogrel or prasugrel."*
13	Pandit 2014	*"No significant differences were reported between cangrelor and clopidogrel in decreasing the primary composite endpoint (death, ischemia-driven revascularization, and MI at 48 hours), all-cause mortality, and MI. No differences were found for severe or fatal bleeding. A significant reduction in ischemia-driven revascularization, stent thrombosis, and Qwave MI was seen in the cangrelor group compared to clopidogrel group."*
14	Sardar 2014	*<u>"Abstract</u>* *Three RCTs included a total of 25,107 participants. Effects of Cangrelor were not different against comparators for myocardial infarction (MI) (Risk ratio [RR] 0.94, 95 % confidence interval [CI] 0.78–1.13) and all-cause mortality (RR 0.72, 95 % CI 0.36–1.43). However, cangrelor significantly reduced the risk of ischemia-driven revascularization (RR 0.72, 95 % CI 0.52–0.98), stent thrombosis*

	Study/Country first author	RESULTS (*Abstract*)
		(RR 0.60, 95 % CI 0.44–0.82) and Qwave MI (RR 0.53, 95 %CI 0.30–0.92) without causing extra major bleeding (Thrombolysis in Myocardial infarction criteria) and severe or life-threatening bleeding (Global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries criteria). Separate analysis against only clopidogrel also showed similar findings except Q wave MI outcome. Use of cangrelor during PCI might reduce the risk of ischemia-driven revascularization and stent thrombosis, without causing extra major bleeding."
15	Verdoia 2014	*Note: ONLY data for cangrelor vs. clopidogrel because the other data is not separated by agent* ***"Conclusion*** *Present meta-analysis shows that the new ADP antagonists prasugrel, ticagrelor, and cangrelor are associated to significant reduction of mortality, reinfarction, RI, and ST respect to clopidogrel alone, without significant increase in bleeding complications and therefore, their use should be strongly advised."*
16	Gouya 2014	***"Results**: In this analysis, 1.3% (286 of 22 116) of patients in DAPT with prasugrel/aspirin or icagrelor/aspirin versus 1.3% (272 of 21 330) in DAPT with clopidogrel/aspirin experienced a stroke event. Accordingly, novel ADP receptor inhibitors on top of aspirin did not reduce the risk of total stroke during a median follow-up of 9.2 months as compared with DAPT with clopidogrel/aspirin (RR, 1.04; 95% CI, 0.88–1.22; P=0.67; I2=0%). In line with this finding, novel ADP receptor inhibitors neither reduced the risk of ischemic stroke (RR, 0.99; 95% CI, 0.82–1.20; P=0.94; I2=0%; Figure 4B) nor increased the risk of intracranial hemorrhage (RR, 1.13; 95% CI, 0.70–1.84; P=0.61; I2=36%; Figure 4C) in the overall study population. However, there was a trend toward higher risk of intracranial hemorrhage in the ticagrelor group (RR, 1.76; 95% CI, 0.89–3.47; P=0.1).* *Secondary Prevention* *During a median follow-up period of 5.6 months, 5.1% (42 of 826) of patients in DAPT with novel ADP receptor blockers (prasugrel/aspirin or ticagrelor/aspirin) versus 2.4% (20 of 844) in DAPT with clopidogrel/ aspirin experienced a stroke event (ischemic stroke, TIA, or intracranial hemorrhage; random-effect model: RR, 3.19; 95% CI, 0.40–25.59; P=0.27; Figure 4D). Significant heterogeneity of the analysis was observed (I2=86%). Although prasugrel resulted in a 10.3-fold higher relative risk of overall stroke in secondary prevention (RR, 10.26; 95% CI, 2.43–43.41; P<0.002), ticagrelor was not associated with a higher risk (RR, 1.22; 95% CI, 0.66–2.26; P=0.54* ***Conclusion**:* *DAPT with prasugrel or ticagrelor and aspirin versus DAPT with clopidogrel and aspirin was not associated with a risk reduction of stroke."*
17	Ronaldson 2012	*"This meta-analysis observed **a trend to lower haemorrhagic potential for ticlopidine plus aspirin compared with clopidogrel plus aspirin** in the post-stenting setting for both the seven randomised controlled trials and the five studies conducted without randomisation, although neither result was significant."*

Appendix E

Table 1. Main Randomized Controlled Trials Included in Previous SR/MAs for Acute Coronary Syndrome

Study	Population	Intervention	Endpoints	Results from Article/Abstract
Clopidogrel versus ticagrelor				
1. Cannon et al[82] (2007) **DISPERSE-2** • Randomized, double-blind, double-dummy trial to assess the **safety, tolerability, and initial efficacy** of AZD6140 plus aspirin in comparison with clopidogrel plus aspirin in patients with NSTE-ACS • 152 sites, 14 countries	NSTE-ACS within the preceding 48 hours, experienced ischemic symptoms of ≥10 min duration at rest, with either biochemical marker evidence of MI or electrocardiographic evidence of schemia **N= 990**	AZD6140 (tica) 90 mg, AZD6140 180 mg, or clopidogrel 300-mg loading dose plus 75 mg once daily for up to **12 weeks** All patients were given aspirin	Primary objective: to assess safety and tolerability by evaluating total bleeding events (major plus minor Bleeding) Additional objectives: 1) individual and composite incidence of MI (including silent MI), death, stroke, and severe recurrent ischemia; and 2) incidence of recurrent schemia during the first 4 to 7 days after randomization	***"Results**: the Kaplan-Meier rate of major or minor bleeding through 4 weeks, was 8.1% in the clopidogrel group, 9.8% in the AZD6140 90-mg group, and 8.0% in the AZD6140 180-mg group (p = 0.43 and p = 0.96, respectively, vs. clopidogrel); the major bleeding rates were 6.9%, 7.1%, and 5.1%, respectively (p = 0.91 and p = 0.35, respectively, vs. clopidogrel). Although not statistically significant, favorable trends were seen in the Kaplan-Meier rates of myocardial infarction (MI) over the entire study period (MI: 5.6%, 3.8%, and 2.5%, respectively; p = 0.41 and p = 0.06, respectively, vs. clopidogrel)* ***Conclusion**: This initial experience with AZD6140 in patients with ACS showed no difference in major bleeding but an increase in minor bleeding at the higher dose with encouraging results on the secondary end point of MI. This agent is currently being studied in a large outcomes trial in 18,000 patients with ACS."*
2. **Wallentin et al[41] (2009)** **PLATO 2009** • Multicenter, prospective, randomized, double-blind, event-driven	Patients hospitalized for ACS with or without ST-segment elevation, with an onset of symptoms in the previous 24 h **N= 18624**	**Ticagrelor group:** loading dose of 180 mg orally, followed by a maintenance dose of 90 mg twice a day, and placebo tablets for clopidogrel	**Primary endpoint**: composite of death from vascular causes, MI, or stroke **Secondary endpoints**: composite of all-cause mortality, MI, or stroke, death from	***"Results:** At **12 months**, the **primary end point**--a composite of death from vascular causes, myocardial infarction, or stroke--had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (**hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001**). Predefined hierarchical testing of secondary end points showed significant*

Study	Population	Intervention	Endpoints	Results from Article/Abstract
trial of patients hospitalized for ACS with or without ST-segment elevation, with an onset of symptoms in the previous 24 h • 862 centers in 43 countries	Duration of treatment: **12 months**	**Clopidogrel group**: loading dose of 300 mg orally followed by a maintenance dose of 75 mg per day, and placebo tablets for ticagrelor All patients were given aspirin 75–100 mg per day unless they were intolerant. Duration: 12 months	vascular causes, MI, stroke, severe recurrent cardiac ischaemia, recurrent cardiac ischaemia, TIA, or other arterial thrombotic event, all-cause mortality; and stent thrombosis. **Safety**: Major bleeding by PLATO criteria and life-threatening/fatal bleeding	*differences in the rates of other composite endpoints, as well as **myocardial infarction** alone (5.8% in the ticagrelor group vs. 6.9% in the clopidogrel group, P=0.005) and **death from vascular causes** (4.0% vs. 5.1%, P=0.001) **but not stroke alone** (1.5% vs. 1.3%, P=0.22). The rate of **death from any cause** was also reduced with ticagrelor (4.5%, vs. 5.9% with clopidogrel; P<0.001). **No significant difference in the rates of major bleeding** was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; P=0.43), but **ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting** (4.5% vs. 3.8%, P=0.03), **including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types**.* ***Conclusion:** In patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding."*
3. Cannon et al[79] (2010) **PLATO (ACS with PCI)** • Randomized double-blind study to	ACS (STEMI or NSTEMI) with planned invasive strategy **N= 13408** of 18624 hospitalized for ACS	Ticagrelor and placebo (180 mg LD followed by 90 mg twice a day), or to clopidogrel and placebo (300–600 mg LD or continuation with maintenance dose	**Primary composite endpoint**: CV death, MI, or stroke **Secondary endpoints**: Individual components of the primary endpoint	***"Results**: The primary composite endpoint occurred in fewer patients in the ticagrelor group than in the clopidogrel group (569 [event rate at 360 days 9.0%] vs 668 [10.7%], hazard ratio 0.84, 95% CI 0.75-0.94; p=0.0025). There was no difference between clopidogrel and ticagrelor groups in the rates of total major bleeding (691 [11.6%] vs 689 [11.5%], 0.99 [0.89-1.10]; p=0.8803) or*

Study	Population	Intervention	Endpoints	Results from Article/Abstract
compare ticagrelor with clopidogrel in patients with a planned invasive strategy for ACS		followed by 75 mg per day) for **6–12 months**. All patients were given aspirin	**Primary safety endpoint**: PLATO defined total major bleeding	*severe bleeding, as defined according to the Global Use of Strategies To Open occluded coronary arteries, (198 [3.2%] vs 185 [2.9%], 0.91 [0.74-1.12]; p=0.3785).* ***Conclusion****: Ticagrelor seems to be a better option than clopidogrel for patients with acute coronary syndromes for whom an early invasive strategy is planned."*
4. **Steg et al**[80] (2010) **PLATO (STEMI with PCI)** • Pre-specified analysis of the PLATO study	STEMI with planned primary PCI or left bundle-branch block **N= 7544** of 18624 ACS patients	Ticagrelor and placebo (180 mg LD followed by 90 mg twice a day), or to clopidogrel and placebo (300–600 mg LD or continuation with maintenance dose followed by 75 mg per day) for **6–12 months**. All patients were given aspirin	**Primary composite endpoint**: CV death, MI, or stroke **Secondary endpoints**: Individual components of the primary endpoint **Primary safety endpoint**: time to first occurrence of any major bleeding event in the total cohort. Assessed separately in the subsets of patients undergoing CABG and/or PCI	***"Results:*** *The reduction of the primary endpoint (myocardial infarction, stroke, or cardiovascular death) with ticagrelor versus clopidogrel (10.8% versus 9.4%; hazard ratio [HR], 0.87; 95% CI, 0.75 to 1.01; P=0.07) was consistent with the overall PLATO results. Ticagrelor reduced several secondary endpoints, including myocardial infarction alone (HR, 0.80; P0.03), total mortality (HR, 0.82; P0.05), and definite stent thrombosis (HR, 0.66; P0.03). The risk of stroke, low in both groups, was higher with ticagrelor (1.7% versus 1.0%; HR 1.63; 95% CI, 1.07 to 2.48; P=0.02). Ticagrelor did not affect major bleeding (HR, 0.98; P=0.76).* ***Conclusion****: In patients with STE-ACS and planned primary percutaneous coronary intervention, the effects of ticagrelor were consistent with those observed in the overall PLATO trial."*
5. **James et al**[44] (2011) **PLATO (ACS with non-invasive treatment strategy)**	ACS with non-invasive management **N= 5216** (28%) of 18624 hospitalized for ACS	Ticagrelor (LD of 180 mg followed by 90 mg twice daily) or clopidogrel (300 mg LD followed by 75 mg daily). All patients were given aspirin	The **primary efficacy endpoint** was the composite of death from vascular causes, myocardial infarction, or stroke. **Secondary endpoints** included the individual	***"Results****: Cumulatively, 3143 (60.3%) patients had been managed non-invasively by the end of follow-up. The incidence of the primary endpoint was lower with ticagrelor than with clopidogrel (12.0% (n=295) v 14.3% (346); HR 0.85, 95% CI 0.73 to 1.00; P=0.04). Overall mortality was also lower (6.1% (147) v 8.2% (195); 0.75, 0.61 to 0.93; P=0.01). The incidence of total major bleeding (11.9%*

Study	Population	Intervention	Endpoints	Results from Article/Abstract
• Pre-specified analysis of the PLATO study • 862 centers in 43 countries			components of the primary end point; all cause mortality; non-vascular mortality; death from vascular causes or myocardial infarction, stroke, severe recurrent cardiac ischaemia, recurrent cardiac ischaemia, transient ischaemic attack, or other arterial thrombotic event; stroke subclassified as ischaemic, haemorrhagic, and unknown. **Primary safety endpoint**: PLATO defined total major bleeding	*(272) v 10.3% (238); 1.17, 0.98 to 1.39; P=0.08) and non-coronary artery bypass grafting related major bleeding (4.0% (90) v 3.1% (71); 1.30, 0.95 to 1.77; P=0.10) was numerically higher with ticagrelor than with clopidogrel* ***Conclusions**: In patients with acute coronary syndrome initially intended for non-invasive management, the benefits of ticagrelor over clopidogrel were consistent with those from the overall PLATO results, indicating the broad benefits of P2Y12 inhibition with ticagrelor regardless of intended management strategy."*
6. **Goto et al**[70] 2015 **PHILO**	ACS with PCI **N=801** Asiatic patients (Japanese, Taiwanese, South Korean)	Ticagrelor (LD of 180 mg followed by 90 mg twice daily) Clopidogrel (300 mg LD followed by 75 mg daily) All patients were given aspirin	**Efficacy**: CV death, MI, stroke **Safety**: time to first occurrence of any major bleeding event	***"Results:** At 12 months, overall major bleeding occurred in 10.3% of ticagrelor-treated patients and in 6.8% of clopidogrel-treated patients (hazard ratio (HR), 1.54; 95% confidence interval (CI): 0.94–2.53); the composite primary efficacy endpoint occurred in 9.0% and in 6.3% of ticagrelor- and clopidogrel-treated patients, respectively (HR, 1.47; 95% CI: 0.88–2.44). For both analyses, the difference between groups was not statistically significant.* ***Conclusion**: In ACS patients from Japan, Taiwan and South Korea, event rates of primary safety and efficacy endpoints were higher, albeit not significantly, in ticagrelor-*

Study	Population	Intervention	Endpoints	Results from Article/Abstract
				treated patients compared with clopidogrel-treated patients. This observation could be explained by the small sample size, imbalance in clinical characteristics and low number of events in the PHILO population."
Clopidogrel versus prasugrel				
7. **Wiviott et al**[76] 2005 **JUMBO–TIMI 26 (NSTE-ACS + SCAD)** • Phase II multicenter, randomized, parallel-group, double-blind, double-dummy, active-comparator-controlled trial	ACS patients undergoing elective or urgent PCI **N= 905**	Prasugrel: • Low-dose (40-mg loading dose followed by 7.5 mg daily), • Intermediate-dose (60-mg loading dose followed by 10 mg daily) • High-dose (60-mg loading dose followed by 15 mg daily) Clopidogrel: • 300-mg loading dose followed by 75 mg daily	**Primary safety endpoint**: non–CABG-related "significant hemorrhage" at 30 days (TIMI major plus minor) **Primary efficacy composite endpoint** (30-day major adverse cardiac events) Secondary endpoints: myocardial infarction, recurrent ischemia, and clinical target vessel thrombosis	***"Results**: Hemorrhagic complications were infrequent, with no significant difference between patients treated with prasugrel or clopidogrel in the rate of significant bleeding (1.7% versus 1.2%; hazard ratio, 1.42; 95% CI, 0.40, 5.08). In prasugrel-treated patients, there were numerically lower incidences of the primary efficacy composite end point (30-day major adverse cardiac events) and of the secondary end points myocardial infarction, recurrent ischemia, and clinical target vessel thrombosis.* ***Conclusions**: In this phase 2 study, which was designed to assess safety when administered at the time of percutaneous coronary intervention, prasugrel and clopidogrel both resulted in low rates of bleeding. The results of this trial serve as* *a foundation for the large phase 3 clinical trial designed to assess both efficacy and safety."*
8. Wiviott et al[42] 2007 **TRITON-TIMI 38 (STEMI+NSTE-ACS)** • RCT, double blind, double dummy design	Moderate- to high-risk ACS patients with planned PCI **N=13608** (10,074 patients with moderate-to-high-risk UA/NSTEMI and 3534 patients with STEMI	Prasugrel: 60 mg LD followed by 10 mg once daily Clopidogrel: 300 mg LD followed by 75 mg daily	**Efficacy**: CV death, MI, stroke **Safety**: Non–CABG-related TIMI major bleeding, non– CABG-related TIMI life-threatening bleeding, and	***"Results**: The primary efficacy endpoint occurred in 12.1% of patients receiving clopidogrel and 9.9% of patients receiving prasugrel (hazard ratio for prasugrel vs. clopidogrel, **0.81**; 95% CI, **0.73 to 0.90; P<0.001**). We also found significant reductions in the prasugrel group in the rates of myocardial infarction (9.7% for clopidogrel vs. 7.4% for prasugrel; P<0.001), urgent target-vessel revascularization (3.7% vs.*

Study	Population	Intervention	Endpoints	Results from Article/Abstract
	Duration of treatment: **6-15 months**	Use of aspirin was required (75 to 162 mg daily)	TIMI major or minor bleeding	*2.5%; P<0.001), and stent thrombosis (2.4% vs. 1.1%; P<0.001). Major bleeding was observed in 2.4% of patients receiving prasugrel and in 1.8% of patients receiving clopidogrel (hazard ratio, 1.32; 95% CI, 1.03 to 1.68; P = 0.03). Also greater in the prasugrel group was the rate of life-threatening bleeding (1.4% vs. 0.9%; P = 0.01), including nonfatal bleeding (1.1% vs. 0.9%; hazard ratio, 1.25; P = 0.23) and fatal bleeding (0.4% vs. 0.1%; P = 0.002).* ***Conclusion****: In patients with acute coronary syndromes with scheduled percutaneous coronary intervention, prasugrel therapy was associated with significantly reduced rates of ischemic events, including stent thrombosis, but with an increased risk of major bleeding, including fatal bleeding. Overall mortality did not differ significantly between treatment groups."*
9. **Montalescot et al**[43] 2009 **TRITON-TIMI 38 subgroup analysis (STEMI with PCI)** • Pre-specified analysis of the TRITON-TIMI 38 • 707 sites in 30 countries	ACS with STEMI and PCI Two strata: (1) patients enrolled within 12h of onset of symptoms (primary PCI); and (2) those enrolled between 12h and 14 days after symptom onset (secondary PCI) N= **2438** (primary PCI) and **1094** (secondary PCI)	Prasugrel (60 mg LD, 10 mg maintenance dose [n=1769]) Clopidogrel (300 mg LD, 75 mg maintenance dose [n=1765])	**Primary endpoint**: CV death, non-fatal MI, or non-fatal stroke **Key secondary efficacy endpoint** was cardiovascular death, non-fatal myocardial infarction, or urgent target vessel revascularisation at 30 days. **Safety endpoint**: TIMI major bleeding that was unrelated to CABG surgery, TIMI life-	***"Results****: At 30 days, 115 (6·5%) individuals assigned prasugrel had met the primary endpoint compared with 166 (9·5%) allocated clopidogrel (hazard ratio 0·68 [95% CI* ***0·54–0·87****]; p=0·0017). This effect continued to 15 months (174 [10·0%] vs 216 [12·4%]; 0·79 [****0·65–0·97****]; p=0·0221). The key secondary endpoint of cardiovascular death, myocardial infarction, or urgent target vessel revascularisation was also significantly reduced with prasugrel at 30 days (0·75 [0·59–0·96]; p=0·0205) and 15 months (0·79 [0·65–0·97]; p=0·0250), as was stent thrombosis. Treatments did not differ with respect to thrombolysis in myocardial infarction (TIMI) major bleeding unrelated to coronary-artery bypass graft (CABG) surgery*

Study	Population	Intervention	Endpoints	Results from Article/Abstract
	Duration of treatment: **15 months**		threatening bleeding (a subset of TIMI major bleeding), TIMI major or minor bleeding, and bleeding receiving transfusion	*at 30 days (p=0·3359) and 15 months (p=0·6451). TIMI life-threatening bleeding and TIMI major or minor bleeding were also similar with the two treatments, and only TIMI major bleeding after CABG surgery was significantly increased with prasugrel (p=0·0033).* ***Conclusion**: In patients with STEMI undergoing PCI, prasugrel is more effective than clopidogrel for prevention of ischaemic events, without an apparent excess in bleeding."*
10. **Roe et al**[46] 2012 **TRILOGY ACS (NSTEMI/UA)** • Double-blind, randomized trial • 800 sites worldwide	UA/NSTEMI selected for medical management **without revascularization** within 10 days after the ACS event N= 7243 Duration of treatment: **30 months** *Note: Prasugrel is only approved in patients with ACS undergoing PCI*	Prasugrel: 30 mg LD followed by 10 mg daily Clopidogrel: 300 mg LD, followed by 75 mg daily Plus aspirin	**Primary endpoint**: composite of CV death, non-fatal MI, or non-fatal stroke **Safety endpoints**: non–CABG-related severe or life-threatening events, major bleeding (TIMI criteria)	***"Results**: the primary end point of death from cardiovascular causes, myocardial infarction, or stroke among patients under the age of 75 years occurred in 13.9% of the prasugrel group and 16.0% of the clopidogrel group (hazard ratio in the prasugrel group, 0.91; 95% confidence interval **[CI], 0.79 to 1.05; P = 0.21**). Similar results were observed in the overall population. The prespecified analysis of multiple recurrent ischemic events (all components of the primary endpoint) suggested a lower risk for prasugrel among patients under the age of 75 years (hazard ratio, 0.85; 95% CI, 0.72 to 1.00; P = 0.04). Rates of severe and intracranial bleeding were similar in the two groups in all age groups. There was no significant between-group difference in the frequency of non-hemorrhagic serious adverse events, except for a higher frequency of heart failure in the clopidogrel group* ***Conclusion**: Among patients with unstable angina or myocardial infarction without ST-segment elevation, prasugrel did not*

Study	Population	Intervention	Endpoints	Results from Article/Abstract
				significantly reduce the frequency of the primary end point, as compared with clopidogrel, and similar risks of bleeding were observed."
11. **Wiviott et al** 2013 **TRILOGY ACS subgroup analysis** • Pre-specified analysis	UA/NSTEMI selected for medical management without revascularization. Assessment of outcomes from the TRILOGY ACS trial based on whether or not patients had coronary angiography before treatment was chosen. *Note: Prasugrel is only approved in patients with ACS undergoing PCI*	Prasugrel: 30 mg LD followed by 10 mg daily Clopidogrel: 300 mg LD, followed by 75 mg daily Plus aspirin	**Primary endpoint**: composite of CV death, non-fatal MI, or non-fatal stroke **Safety endpoints**: non–CABG-related severe or life-threatening events, major bleeding (TIMI criteria)	***"Results**: 7243 patients younger than 75 years were included in the TRILOGY ACS primary analysis. 3085 (43%) had angiography at baseline, 4158 (57%) had not. Fewer patients who had angiography reached the primary endpoint at 30 months compared with those who did not have angiography, according to Kaplan-Meier analysis (281/3085 [12·8%] vs 480/4158 [16·5%], adjusted hazard ratio [HR] 0·63, 95% CI 0·53–0·75; p<0·0001). The proportion of patients who reached the primary endpoint was lower in the prasugrel group than in the clopidogrel group for those who had angiography (122/1524 [10·7%] vs 159/1561 [14·9%], HR 0·77, 95% CI 0·61–0·98; p=0·032) but did not differ between groups in patients who did not have angiography (242/2096 [16·3%] vs 238/2062 [16·7%], HR 1·01, 0·84–1·20; p=0·94; p interaction=0·08). Overall, TIMI major bleeding and GUSTO severe bleeding were rare. Bleeding outcomes tended to be higher with prasugrel but did not differ significantly between treatment groups in either angiography cohort.* ***Conclusion**: Among patients who had angiography who took prasugrel there were fewer cardiovascular deaths, myocardial infarctions, or strokes than in those who took clopidogrel. This result needs to be corroborated, but it is consistent with previous trials of more versus less intensive*

Study	Population	Intervention	Endpoints	Results from Article/Abstract
				antiplatelet treatment. When angiography is done for acute coronary syndrome and anatomic coronary disease confirmed, the benefits and risks of intensive antiplatelet treatment exist whether the patient is treated with drugs or percutaneous coronary intervention."
12. **De Servi et al**[75] 2014 **TRITON-TIMI 38 subgroup analysis (NSTE-ACS with PCI)** • Not pre-specified analysis	NSTE-ACS with planned PCI N= 10074	Prasugrel: 60 mg LD followed by 10 mg once daily Clopidogrel: 300 mg LD followed by 75 mg daily	**Efficacy**: CV death, MI, stroke **Safety**: Non–CABG-related TIMI major bleeding	***"Results**: The primary endpoint was significantly reduced by prasugrel in the overall NSTE-ACS population (hazard ratio (HR) 0.82, 95% confidence interval (CI) 0.73-0.93, p=0.002) as well as in unstable angina (UA) and in non-ST elevation myocardial infarction (NSTEMI) patient subgroups (interaction p value=0.39). Although non-coronary artery bypass graft (CABG) TIMI major bleeding was increased with prasugrel as compared with clopidogrel (HR 1.40, 95% CI 1.05-1.88, p=0.02), there was a net clinical benefit in patients assigned to prasugrel (HR 0.89, 95% CI 0.80-1.00, p=0.043), which was consistent for UA and NSTEMI subgroups (interaction p value=0.84 and 0.72).* ***Conclusion**: Prasugrel, as compared with clopidogrel, significantly reduced the primary endpoint of the TRITON-TIMI 38 trial in NSTE-ACS patients, as well as in the UA and NSTEMI groups."*
Prasugrel versus ticagrelor				
13. **Motovska et al**[72] 2016 **PRAGUE-18** • Multicenter, randomized, open-label, phase-IV,	Patients with acute myocardial infarction treated with PCI N= 1,230	Prasugrel: 60 mg LD, followed by 10 mg once daily Ticagrelor: LD of 180 mg followed by 90 mg twice daily	**Primary endpoint**: a composite of all-cause death, reinfarction, stroke, serious bleeding requiring transfusion or prolonging hospitalization, or urgent target vessel	***"Results**: The study was prematurely terminated for futility. The occurrence of the primary end point did not differ between groups receiving prasugrel and ticagrelor (4.0% and 4.1%, respectively; odds ratio, 0.98; 95% confidence interval, 0.55–1.73; P=0.939). No significant difference was found in any of the components of the primary end*

Study	Population	Intervention	Endpoints	Results from Article/Abstract
controlled trial • 14 centers in Czech Republic			revascularization within 7 days after randomization or at discharge if before the seventh day **Key secondary endpoint**: a composite of cardiovascular death, nonfatal myocardial infarction, or stroke during the follow-up period **Safety endpoint**: bleeding occurrences	*point. The occurrence of key secondary end point within 30 days, composed of cardiovascular death, nonfatal myocardial infarction, or stroke, did not show any significant difference between prasugrel and ticagrelor (2.7% and 2.5%, respectively; odds ratio, 1.06; 95% confidence interval, 0.53–2.15; P=0.864).* ***Conclusion**: This head-to-head comparison of prasugrel and ticagrelor does not support the hypothesis that one is more effective or safer than the other in preventing ischemic and bleeding events in the acute phase of myocardial infarction treated with a primary percutaneous coronary intervention strategy. The observed rates of major outcomes were similar but with broad confidence intervals around the estimates. These interesting observations need to be confirmed in a larger trial."*
Clopidogrel versus cangrelor				
14. **Harrington et al**[97] 2009 **CHAMPION PCI** • Randomized, double-blind, double-dummy, active-control trial	ACS with PCI N= 8716 patients underwent PCI Follow-up: 30 days	Cangrelor 30 µg/kg bolus 30 min before PCI and 4 µg/kg/min 2h Clopidogrel 600 mg 30min before PCI	**Primary efficacy endpoint**: composite of death from any cause, myocardial infarction, or IDR at 48 hours **Safety endpoint**: bleeding (GUSTO criteria)	***"Conclusion**: Cangrelor, when administered intravenously 30 minutes before PCI and continued for 2 hours after PCI, was not superior to an oral loading dose of 600 mg of clopidogrel, administered 30 minutes before PCI, in reducing the composite end point of death from any cause, myocardial infarction, or ischemia-driven revascularization at 48 hours."*
15. **Bhatt et al** 2009 **CHAMPION PLATFORM**	Patients undergoing PCI NSTEMI: 60% UA: 35%	Cangrelor IV 30 ug/kg bolus, 4 ug/kg/min 2-4 h, then clopidogrel 600 mg	**Efficacy:** Death/MI/IDR **Safety**: bleeding	***"Conclusion:** The use of periprocedural cangrelor during PCI was not superior to placebo in reducing the primary end point. The prespecified secondary end points of stent thrombosis and death were lower in*

Study	Population	Intervention	Endpoints	Results from Article/Abstract
	SCAD: 5% N= 5382 Follow-up: 30 days	Clopidogrel 600 mg at the end of PCI		*the cangrelor group, with no significant increase in the rate of transfusion. Further study of intravenous ADP blockade with cangrelor may be warranted."*
16. **Bhatt et al**[96] 2013 **CHAMPION PHOENIX** • Randomized, double-blind, double-dummy, active-control trial	Patients undergoing PCI STEMI: 18% NSTEMI: 26%, SCAD: 56% Follow-up: 48 hours	Cangrelor IV 30 mg/kg bolus and 4 µg/kg/min 2-4 h, Clopidogrel 600 or 300 mg LD	**Efficacy**: Death/MI/IDR/ST **Safety**: severe bleeding not related to CABG (GUSTO criteria)	***"Results**: The rate of the primary efficacy end point was 4.7% in the cangrelor group and 5.9% in the clopidogrel group (adjusted odds ratio with cangrelor, 0.78; 95% confidence interval [CI], **0.66 to 0.93**; P = 0.005). The rate of the primary safety end point was 0.16% in the cangrelor group and 0.11% in the clopidogrel group (odds ratio, 1.50; 95% CI, 0.53 to 4.22; P = 0.44). Stent thrombosis developed in 0.8% of the patients in the cangrelor group and in 1.4% in the clopidogrel group (odds ratio, 0.62; 95% CI, **0.43 to 0.90**; P = 0.01). The rates of adverse events related to the study treatment were low in both groups, though transient dyspnea occurred significantly more frequently with cangrelor than with clopidogrel (1.2% vs. 0.3%). The benefit from cangrelor with respect to the primary end point was consistent across multiple prespecified subgroups.* ***Conclusion**: Cangrelor significantly reduced the rate of ischemic events, including stent thrombosis, during PCI, with no significant increase in severe bleeding."*

Abbreviations: ACS, Acute Coronary Syndrome; CAD, coronary artery disease; can, cangrelor; clo, clopidogrel; DAPT, dual antiplatelet therapy; MA, meta-analysis; MI, myocardial infarction; NSTE-ACS, non-ST-elevation acute coronary syndrome; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; pra, prasugrel; RCT, randomized controlled trial; STEMI, ST-elevation myocardial infarction; TIA, transient ischemic stroke; tica, ticagrelor; ticlo, ticlopidine; UA, unstable angina

Appendix F

Table 1. Randomized Controlled Trials Not Included in Previous SR/MAs for Acute Coronary Syndrome

Study	Population	Intervention	Endpoints	Results from Article/Abstract
Clopidogrel versus ticagrelor				
Tang et al 2016[69] • RCT • Zhujiang Hospital, China	STEMI undergoing PCI N= 400	Clo vs. tica	MACCE (composite of overall death, MI), unplanned revascularization, or stroke), stent thrombosis, and the composite end point of CV death, nonfatal MI, and stroke	***"Results**: Compared with the clopidogrel-treated group, ticagrelor treatment significantly reduced the incidence of MACCE [5 vs. 14; odds ratio (OR), 0.341; 95% confidence interval (CI), 0.120-0.964; P = 0.034] and the composite end points of cardiovascular death, nonfatal MI, and stroke (4 vs. 13; OR, 0.294; 95% CI, 0.094-0.916; P = 0.026). Fewer patients in the ticagrelor group received GPIIb/IIIa inhibitors after PPCI compared with those in the clopidogrel group (10 vs. 21; OR, 0.449; 95% CI, 0.206-0.979; P = 0.040). However, there were no significant differences between the groups in the incidences of all-cause mortality, nonfatal MI, unplanned revascularization, stroke, stent thrombosis (P = 0.522, P = 0.246, P = 0.246, P = 0.217, P = 0.246, respectively), or bleeding events (10 vs. 7; OR, 1.451; 95% CI, 0.541-3.891; P = 0.457).* ***Conclusion**: Among patients with STEMI undergoing PPCI, ticagrelor reduces the incidence of MACCE and the composite end point of cardiovascular death, nonfatal MI, and stroke compared with clopidogrel. Ticagrelor also reduces the need for GPIIb/IIIa inhibitors. However, no significant difference was observed in the risk of bleeding between the 2 groups."*

Abbreviations: clo, clopidogrel; MACCE, major adverse cardiovascular and cerebrovascular event, MI, myocardial infarction; STEMI, ST-elevation myocardial infarction; tica, ticagrelor

Appendix G

Table 1. List of Excluded References

Wrong study design	
1.	Chandrasekhar J, Hibbert B, Froeschl M, So D, Mehran R, May ML. The impact of switching P2Y12 receptor inhibitor therapy during index hospitalization: A systematic review. European Journal of Clinical Pharmacology. 2016;72(1):83-91.
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